



Peginterferon/Ribavirin-Experienced, Genotype 4 Patient...
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Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy	12 weeks	Ia, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	Ia, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin ^c	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin	16 weeks	Ia, B
Daily ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	Ia, B
^a For decompensated cirrhosis , please refer to the appropriate section. ^b This is a 3-tablet coformulation. Please refer to the prescribing information. ^c Please see statement on FDA <u>warning</u> regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.		

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). The study included 116 patients with genotype 4 infection. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients and 27 with compensated cirrhosis (Feld, 2015).



Peginterferon/Ribavirin-Experienced, Genotype 4 Patient...
From www.HCVGuidance.org on March 19, 2018

Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naïve (n=66) and -experienced (n=37) patients with genotype 4 infection (Asselah, 2015). The overall SVR12 rate among treatment-experienced, genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. However, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the nonribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach and is an alternative recommendation.

Glecaprevir/Pibrentasvir

The phase 3, single-arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis (Forns, 2017). Overall, 25% of patients were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). All 16 patients with genotype 4 infection (unknown number with prior treatment experience) achieved SVR.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

The AGATE-I trial randomized 120 treatment-naïve or -experienced patients (interferon-based regimens) with genotype 4 infection and compensated cirrhosis to 12 weeks or 16 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a).

The phase 3, open-label, partly randomized AGATE-II trial included a cohort of 60 treatment-naïve or -experienced (interferon-based regimens), genotype 4-infected patients with compensated cirrhosis. These participants were randomized to 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rate from the 12-week arm was 97%.

These data support the use of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with compensated cirrhosis (Esmat, 2015a). Due to the number of treatment options that exist, including those that do not use ribavirin, this is an alternative rather than a recommended option.

Ledipasvir/Sofosbuvir + Ribavirin

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study (Kohli, 2015). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 rate of 94% (32/34) in treatment-experienced patients with genotype 4



Peginterferon/Ribavirin-Experienced, Genotype 4 Patient...
From www.HCVGuidance.org on March 19, 2018

infection ([Asselah, 2016](#)). Due to the small number of patients overall and with cirrhosis, the addition of ribavirin to the 12-week regimen is recommended in patients with cirrhosis ([Kohli, 2015](#)). This is an alternative regimen due to the need for ribavirin.

Last update: September 21, 2017



DAA-Experienced (Including NS5A Inhibitors), Genotype 4...
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DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients, With or Without Compensated Cirrhosis

Recommended regimen for: DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients, With or Without Compensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A
^a For <u>decompensated cirrhosis</u> , please refer to the appropriate section.		

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 4 infection, with or without compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The trials included 22 genotype 4-infected patients with a prior treatment failure with an NS5A inhibitor-containing DAA regimen, and 19 genotype 4-infected patients with a prior treatment failure with a DAA regimen not containing an NS5A inhibitor. The study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for 12 weeks in these patients. Overall, 46% of patients in these clinical trials had compensated cirrhosis, although the number of genotype 4-infected patients with cirrhosis was not provided. Among the 22 patients who had a prior treatment failure with an NS5A inhibitor-containing regimen, 91% (20/22) achieved SVR; 1 patient relapsed and another experienced treatment failure for nonvirologic reasons. All patients with a history of treatment failure with a DAA regimen not containing an NS5A inhibitor achieved SVR (19/19, 100%) ([Boutiere, 2017](#)).

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Treatment-Experienced Genotype 5 or 6
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Treatment-Experienced Genotype 5 or 6

The following pages include guidance for management of treatment-experienced patients with genotype 5 or 6 infection.

- [Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis](#)
- [DAA-Experienced \(Including NS5A Inhibitors\), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis](#)

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Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Pa...
From www.HCVGuidance.org on March 19, 2018

Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b for patients without cirrhosis	8 weeks	Ia, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b for patients with compensated cirrhosis	12 weeks	I, B
Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	Ia, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	Ia, B
^a For <u>decompensated cirrhosis</u> , please refer to the appropriate section. ^b This is a 3-tablet coformulation. Please refer to the prescribing information.		

Recommended Regimens

Glecaprevir/Pibrentasvir

A combined analysis of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 8 weeks or 12 weeks among 1,904 patients participating in phase 2 and phase 3 clinical trials included 30 patients with genotype 5 infection and 41 with genotype 6 infection (Puoti, 2017). Approximately 21% to 26% of patients in the overall study had a prior interferon-based treatment failure (DAA failure was excluded); no patients had cirrhosis. SVR among treatment-naïve or -experienced, genotype 5-infected participants was 100% (2/2) for those receiving 8 weeks of glecaprevir/pibrentasvir and 100% (28/28) for those receiving 12 weeks of glecaprevir/pibrentasvir. SVR rates among treatment-naïve or -experienced, genotype 6-infected participants were 90% (9/10) for those receiving 8 weeks of glecaprevir/pibrentasvir and 100% (31/31) among those receiving 12 weeks of glecaprevir/pibrentasvir. The single treatment failure in the 8-week group was a nonvirologic failure.

Ledipasvir/Sofosbuvir

Ledipasvir has in vitro activity against most genotype 6 subtypes, except 6e (Wong, 2013); (Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in treatment-naïve or -experienced patients with genotype 6



Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Pa...

From www.HCVGuidance.org on March 19, 2018

infection. Twenty-five patients (92% treatment naive) who were primarily of Asian descent (88%) were infected with different genotype 6 subtypes (n=8 6a; n=6 6e; n=3 6l; n=2 6m; n=3 6p; n=2 6q; n=1 6r). Two patients (8%) had compensated cirrhosis. The SVR12 rate was 96% (24/25). The single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events ([Gane, 2015](#)).

Similarly, 41 patients with genotype 5 infection were treated with 12 weeks of ledipasvir/sofosbuvir. The group included both treatment-naïve and -experienced patients, with and without cirrhosis. The SVR was 93% (38/41) ([Abergel, 2016](#)).

Sofosbuvir/Velpatasvir

Velpatasvir has in vitro activity against genotypes 5 and 6. The ASTRAL-1 study included 35 patients with genotype 5 infection and 41 patients with genotype 6 infection. Among those participants, only 11 and 3, respectively, were treatment experienced ([Feld, 2015](#)). All genotype 5 and 6, treatment-experienced patients treated with 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) achieved SVR12.

Last update: September 21, 2017



DAA-Experienced (Including NS5A Inhibitors), Genotype 5...
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DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Recommended regimen for:		
DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING ¹
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	Ila, B
^a For <u>decompensated cirrhosis</u> , please refer to the appropriate section.		

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

Minimal data are available from phase 3 clinical trials regarding the efficacy of a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) among patients with genotype 5 or 6 infection with a history of treatment failure with a DAA-containing regimen. All 7 patients with genotype 5 or 6 infection (1 genotype 5; 6 genotype 6) participating in the phase 3 POLARIS-1 trial achieved SVR. All participants enrolled in the study had a prior treatment failure with an NS5A inhibitor-containing regimen. Forty-six percent had compensated cirrhosis, although the percentage of patients with genotype 5 or 6 infection with cirrhosis was not provided (Bourliere, 2017).

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Management of Unique Populations with HCV Infection
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Management of Unique Populations with HCV Infection

The following pages include guidance for management of patients with HCV in unique populations.

- [Patients With HIV/HCV Coinfection](#)
- [Patients With Decompensated Cirrhosis](#)
- [Patients Who Develop Recurrent HCV Infection Post Liver Transplantation](#)
- [Patients With Renal Impairment](#)
- [Kidney Transplant Patients](#)
- [Management of Acute HCV Infection](#)
- [HCV in Pregnancy](#)
- [HCV in Children](#)

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Patients With HIV/HCV Coinfection

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Patients With HIV/HCV Coinfection

This section provides guidance on the treatment of chronic HCV infection in HIV/HCV-coinfected patients. For individuals with acute HCV infection, please refer to the [Acute HCV](#) section. HIV/HCV-coinfected patients suffer from more liver-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than HCV-monoinfected patients ([Lo Re, 2014](#)); ([Chen, 2009](#)). Even in the potent HIV antiretroviral therapy era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HIV/HCV coinfection ([Thein, 2008a](#)); ([de Ledinghen, 2008](#)); ([Ejler, 2013](#)); ([Kirk, 2013](#)). As such, treatment of HCV in HIV-infected patients should be a priority for providers, payers, and patients. However, if HCV treatment is delayed for any reason, liver disease progression should be monitored at routine intervals as recommended in the guidance (see [When and in Whom to Initiate Therapy recommendation for repeat liver disease assessment](#)).

Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with peginterferon/ribavirin have lower rates of hepatic decompensation, hepatocellular carcinoma, and liver-related mortality ([Berenguer, 2009](#)); ([Limketkai, 2012](#)); ([Mira, 2013](#)). Uptake of HCV therapy was lower in the HIV/HCV-coinfected population owing to historically lower response rates, patient comorbidities, patient and practitioner perceptions, and adverse events associated with interferon-based therapy ([Mehla, 2006a](#)); ([Thomas, 2008](#)).

With the availability of HCV direct-acting antivirals (DAAs), efficacy and adverse event rates among those with HIV/HCV coinfection are similar to those observed with HCV monoinfection ([Bhattacharya, 2017](#)); ([Naggle, 2015](#)); ([Sulkowski, 2015](#)); ([Wyles, 2015](#)); ([Wyles, 2017b](#)) and many prior barriers have diminished. However, treatment of HIV/HCV-coinfected patients requires continued awareness and attention to the complex drug-drug interactions that can occur between DAAs and antiretroviral medications. Drug interactions with DAAs and antiretroviral agents are summarized in the text and tables of this section as well as in the US Department of Health and Human Services HIV treatment guidelines (<https://aidsinfo.nih.gov/guidelines>). Another resource for screening for drug-drug interactions with DAAs is the University of Liverpool website (www.hep-druginteractions.org).

Risk for Hepatitis B Virus Reactivation

Due to shared modes of transmission, HIV/HCV-coinfected patients are also at risk for hepatitis B virus (HBV) infection. Reactivation of HBV has been reported in patients starting DAA HCV therapy who are not on active HBV agents. Consistent with general recommendations for the assessment of both HIV- and HCV-infected patients, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc testing. HIV-infected patients who have evidence of HBV infection should be on antiretroviral agents with activity against HBV, preferably tenofovir disoproxil fumarate or tenofovir alafenamide. For patients who are only anti-HBc positive and not on tenofovir-based antiretroviral therapy, subsequent monitoring for HBV reactivation should be as detailed in the [Monitoring](#) section of the guidance.



Patients With HIV/HCV Coinfection
From www.HCVGuidance.org on March 19, 2018

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications	
RECOMMENDED	RATING
Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.	I, A
Daclatasvir when used in combination with other antivirals Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (decrease to 30 mg/d), cobicistat-boosted atazanavir (decrease to 30 mg/d), elvitegravir/cobicistat (decrease to 30 mg/d), and efavirenz or etravirine (increase to 90 mg/d).	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)^a Glecaprevir/pibrentasvir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir. Given the limited data on the safety of elvitegravir/cobicistat with glecaprevir/pibrentasvir, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients.	IIa, B
Simeprevir used in combination with other antivirals Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, dolutegravir, rilpivirine, and tenofovir.	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) Sofosbuvir/velpatasvir can be used with most antiretrovirals, but not efavirenz, etravirine, or nevirapine. Because velpatasvir has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. Due to limited experience with this drug combination, renal monitoring is recommended during the dosing period. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) Ledipasvir/sofosbuvir can be used with most antiretrovirals. Because this therapy increases tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min.	IIa, C



Patients With HIV/HCV Coinfection
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Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications	
The absolute tenofovir levels are highest, and may exceed exposures for which there are established renal safety data, when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens. Due to lack of sufficient safety data with this drug combination, consideration should be given to changing the antiretroviral regimen. If the combination is used, renal monitoring is recommended during the dosing period. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	
For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.	Ila, C
<p>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)</p> <p>Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir.</p> <p>The dose of ritonavir used for boosting atazanavir should be held when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. Atazanavir (300 mg) should be administered at the same time as the fixed-dose HCV combination.</p>	Ila, C
<p>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)</p> <p>Sofosbuvir/velpatasvir/voxilaprevir should be used with antiretroviral drugs with which they do not have substantial interactions: dolutegravir, emtricitabine, enfuvirtide, lamivudine, rilpivirine, and raltegravir.</p> <p>Given increases in voxilaprevir AUC with darunavir/ritonavir or elvitegravir/cobicistat coadministration and lack of clinical safety data, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients.</p> <p>Because this therapy has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. In patients receiving sofosbuvir/velpatasvir/voxilaprevir and tenofovir disoproxil fumarate concomitantly, renal monitoring is recommended during the dosing period.</p>	Ila, B
^a This is a 3 tablet coformulation. Please refer to the prescribing information.	



Patients With HIV/HCV Coinfection
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Regimens Not Recommended for Patients with HIV/HCV Coinfection	
NOT RECOMMENDED	RATING
Antiretroviral treatment interruption to allow HCV therapy is not recommended.	III, A
Elbasvir/grazoprevir should not be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B
Glecaprevir/pibrentasvir should not be used with atazanavir, ritonavir-containing antiretroviral regimens, efavirenz, or etravirine.	III, B
Sofosbuvir/velpatasvir should not be used with efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir/velpatasvir/voxilaprevir should not be used with ritonavir-boosted atazanavir, efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir-based regimens should not be used with tipranavir.	III, B
Paritaprevir/ritonavir/ombitasvir plus dasabuvir should not be used with darunavir, efavirenz, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, etravirine, nevirapine, cobicistat, or rilpivirine.	III, B
Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should not be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.	III, B
Ribavirin should not be used with didanosine, stavudine, or zidovudine.	III, B
Simeprevir should not be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B

Clinical Trial, Pharmacokinetic, and Drug Interaction Data

Extensive recommendations for antiretroviral therapy use, including for persons anticipating HCV treatment, are available at jama.jamanetwork.com and aidsinfo.nih.gov.

Antiretroviral drug switches may be performed to allow compatibility with DAAs with the goal of maintaining HIV suppression without compromising future options. Considerations include prior treatment history, responses to antiretroviral therapy, resistance profiles, and drug tolerance (Günthard, 2014); (DHHS, 2017). Treatment interruption in HIV/HCV-coinfected individuals is not recommended as it is associated with increased cardiovascular events (SMART, 2006) and increased rates of fibrosis progression and liver-related events (Tedaldi, 2008); (Thorpe, 2011). The availability of multiple effective HCV DAA and HIV antiretroviral regimens makes it possible for all HIV/HCV-coinfected patients to safely and successfully receive HCV treatment. Switching an optimized antiretroviral regimen carries risks, including adverse effects and HIV viral breakthrough (Eron, 2010). HIV viral breakthrough is a particular concern for those with substantial antiretroviral experience or known resistance to antiretroviral drugs. If necessary, antiretroviral therapy switches should be done in close collaboration with the treating HIV provider prior to HCV treatment initiation.

Although fewer HIV/HCV-coinfected patients than HCV-monoinfected patients have been treated in DAA trials, efficacy rates to date have been remarkably similar between the groups (Sulkowski, 2013); (Sulkowski, 2014); (Dieterich, 2014b); (Rodríguez-Torres, 2015); (Osinusi, 2015); (Sulkowski, 2015); (Dieterich, 2015); (Naggie, 2015); (Wyles, 2015). Thus, results from HCV monoinfection studies largely justify the recommendations for HIV/HCV coinfection (discussed in the *Initial Treatment* and *Retreatment* sections). Discussion specific to studies of HIV/HCV coinfection is included here.



Patients With HIV/HCV Coinfection

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Daclatasvir + Sofosbuvir

The phase 3 ALLY-2 study evaluated the 12-week regimen of daclatasvir plus sofosbuvir in patients with HIV/HCV coinfection with genotype 1, 2, 3, or 4 ([Wyles, 2015](#)). This open-label clinical trial enrolled both treatment-naïve ($n=151$) and -experienced ($n=52$) HIV/HCV-coinfected patients. Treatment-naïve patients were randomly assigned (2:1), with stratification by cirrhosis status and genotype, to receive 12 weeks or 8 weeks of once-daily daclatasvir (60 mg dose adjusted based on antiretroviral regimen) and sofosbuvir (400 mg). Treatment-experienced patients received daclatasvir and sofosbuvir for 12 weeks. Genotype distribution was 83%, 9%, 6%, and 2% of patients, respectively, for genotype 1, 2, 3, and 4 HCV infection; 14% of all participants had compensated cirrhosis. Antiretroviral drugs allowed were ritonavir-boosted darunavir, atazanavir, or lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir.

The combination of daclatasvir and sofosbuvir once daily for 12 weeks achieved SVR12 in 97% of HIV/HCV-coinfected patients with genotype 1, 2, 3, or 4 infection, and was safe and well tolerated. Ninety-seven percent of treatment-naïve patients and 98% of treatment-experienced patients achieved SVR. However, among patients who received 8 weeks of therapy, only 76% of patients achieved SVR. Factors associated with relapse in this patient group included high baseline HCV RNA level (>2 million IU/mL; 69%), concomitant use of a boosted darunavir-based antiretroviral regimen with 30 mg of daclatasvir (67%), and the presence of compensated cirrhosis (60%).

Pharmacology and Drug Interaction Data

Daclatasvir is metabolized by cytochrome P450 (CYP) 3A4 and is therefore susceptible to drug interactions with potent inducers and inhibitors of this enzyme ([Eley, 2014](#)). The dose of daclatasvir should be increased from 60 mg to 90 mg when used with efavirenz, etravirine, or nevirapine ([Bifano, 2013](#)). The dose of daclatasvir should be decreased from 60 mg to 30 mg when used with ritonavir-boosted atazanavir, cobicistat-boosted atazanavir, or elvitegravir/cobicistat ([Smolders, 2017](#)). A daclatasvir dose of 60 mg should be used with ritonavir-boosted darunavir and ritonavir-boosted lopinavir ([Gandhi, 2015](#)).

Elbasvir/Grazoprevir

The safety, tolerability, and efficacy of the second-generation NS3/4A serine protease inhibitor grazoprevir (MK-5172) plus the NS5A inhibitor elbasvir (MK-8742) were assessed in patients with HIV/HCV coinfection in the C-EDGE COINFECTION study. C-EDGE COINFECTION was a phase 3, nonrandomized, open-label, single-arm study in which treatment-naïve patients with genotype 1, 4, or 6 infection and HIV coinfection, with or without compensated cirrhosis, were enrolled in Europe, the US, and Australia ([Rockstroh, 2015](#)). All patients were either naïve to treatment with any antiretroviral therapy (ART) with a CD4 cell count $>500/\text{mm}^3$ ($n=7$), or stable on current ART for at least 8 weeks with a CD4 cell count $>200/\text{mm}^3$ ($n=211$) and undetectable HIV RNA. All 218 enrolled patients received the once-daily fixed-dose combination of elbasvir (50 mg) plus grazoprevir (100 mg) for 12 weeks. All 218 patients completed follow-up at week 12. The median baseline CD4 cell count was 568 (424-626)/ mm^3 . Limited antiretrovirals were allowed, specifically a nucleoside/nucleotide backbone of abacavir (21.6%) versus tenofovir (75.2%), in combination with raltegravir (52%), dolutegravir (27%), or rilpivirine (17%).

SVR12 was achieved by 96% (210/218) of patients (95% CI, 92.9-98.4). One patient did not achieve SVR12 for a nonvirologic reason and 7 patients without cirrhosis relapsed (2 subsequently confirmed as reinfections, highlighting the requirement of continued harm-reduction strategies after SVR). Thirty-five patients with compensated cirrhosis achieved SVR12. The most common adverse events were fatigue (13%; 29), headache (12%; 27), and nausea (9%; 20). No patient discontinued treatment because of an adverse event. Three out of 6 patients who relapsed before SVR12 had NS3 and/or NS5A resistance-associated substitutions (RASs) while the others had wild type virus at the time of relapse. Two patients receiving ART had transient HIV viremia but subsequently returned to undetectable levels without a change in ART. No significant changes were observed with CD4 cell counts or new opportunistic infections. Elbasvir/grazoprevir without ribavirin seems to be effective and well tolerated among patients coinfecting with HIV, with or without compensated cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population ([Zeuzem, 2017](#)).



Patients With HIV/HCV Coinfection
From www.HCVGuidance.org on March 19, 2018

Pharmacology and Drug Interaction Data

Elbasvir is a substrate for CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Grazoprevir is a substrate for CYP3A4, P-gp, and the liver uptake transporter OATP1B1. Moderate and strong CYP3A and P-gp inducers (including efavirenz) are not recommended for coadministration with elbasvir/grazoprevir. OATP1B1 inhibitors are also not recommended with grazoprevir.

Elbasvir/grazoprevir is not compatible with any ritonavir- or cobicistat-boosted HIV protease inhibitor, elvitegravir/cobicistat, efavirenz, or etravirine (Feng, 2016).

Glecaprevir/Pibrentasvir

The safety and efficacy of glecaprevir (ABT-493), a pangenotypic NS3/4A protease inhibitor, coformulated with pibrentasvir (ABT-530), a pangenotypic NS5A inhibitor, were evaluated in the phase 3, multicenter EXPEDITION-2 study (Rockstroh, 2017). This study evaluated 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in 137 HIV/HCV-coinfected adults without cirrhosis and 12 weeks of glecaprevir/pibrentasvir in 16 HIV/HCV-coinfected patients with compensated cirrhosis. Treatment-naïve and -experienced patients with genotype 1, 2, 3, 4, or 6 infection were enrolled. Patients were either antiretroviral naïve with a CD4 cell count $\geq 500/\text{mm}^3$, or on a stable ART regimen for at least 8 weeks with a CD4 cell count $\geq 200/\text{mm}^3$. ART drugs included raltegravir, dolutegravir, rilpivirine, tenofovir disoproxil fumarate, tenofovir alafenamide, abacavir, emtricitabine, and lamivudine. One patient received elvitegravir/cobicistat. Overall SVR12 was 98% (136/136 among those without cirrhosis on the 8-week regimen, and 14/15 in those with compensated cirrhosis on the 12-week regimen). Four serious adverse events were reported, none of which were DAA related. One of these led to treatment discontinuation.

Pharmacology and Drug Interaction Data

Glecaprevir and pibrentasvir area under the curve (AUC) are increased roughly 3-fold and 1.57-fold, respectively, with tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat (Kosloski, 2017). Only 1 patient received this combination in the EXPEDITION-2 study. Although the increases in AUC of glecaprevir and pibrentasvir when coadministered with elvitegravir/cobicistat are not considered clinically relevant by the manufacturer or the US Food and Drug Administration (FDA), due to lack of sufficient clinical safety data, close monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Consider liver enzyme testing every 4 weeks. Ritonavir-boosted protease inhibitors are not recommended with glecaprevir/pibrentasvir.

Glecaprevir and pibrentasvir AUCs are reduced 25% and 27%, respectively, with abacavir/lamivudine/dolutegravir. These reductions are unlikely to have clinical relevance. Raltegravir and rilpivirine AUCs are increased 47% and 84%, respectively, with glecaprevir/pibrentasvir (Oberoi, 2016). These interactions do not require dose adjustment. Forty-five and 32 individuals received raltegravir or rilpivirine, respectively, in the EXPEDITION-2 study.

Glecaprevir absorption is pH dependent and glecaprevir exposures are reduced approximately 50% with 40 mg of omeprazole daily.

Ledipasvir/Sofosbuvir

The safety and efficacy of 12 weeks of ledipasvir/sofosbuvir were evaluated in the phase 2, single-center, open-label ERADICATE trial, which included 50 HIV/HCV-coinfected patients with genotype 1 infection who were treatment naïve without cirrhosis (Qsinusi, 2015). Thirteen patients were not receiving antiretroviral therapy and 37 patients were on protocol-allowed medications (tenofovir, emtricitabine, rilpivirine, raltegravir, and efavirenz). Although the inclusion criteria for patients receiving antiretroviral therapy allowed CD4 cell counts $>100/\text{mm}^3$, the median CD4 cell count was $576/\text{mm}^3$. Overall, 98% achieved SVR12 (13/13 in the treatment-naïve arm and 36/37 in the treatment-experienced arm). There were no deaths, discontinuations, or clinically significant, serious adverse events. Renal function was monitored frequently



Patients With HIV/HCV Coinfection

From www.HCVGuidance.org on March 19, 2018

during this trial and after administration of study drugs using a battery of tests (serum creatinine, eGFR, urinary beta-2 microglobulin, and urine protein and glucose). No clinically significant changes in these parameters or renal toxicity were observed.

A larger study, ION-4, reported similar outcomes with ledipasvir/sofosbuvir ([Naggie, 2015](#)). A total of 335 HCV treatment-naïve and -experienced HIV/HCV-coinfected patients were enrolled in the study and received ledipasvir/sofosbuvir once daily for 12 weeks. Patients received tenofovir disoproxil fumarate and emtricitabine with raltegravir (44%), efavirenz (48%), or rilpivirine (9%). Genotypes included were 1a (75%), 1b (23%), and 4 (2%). Twenty percent of patients had compensated cirrhosis, 34% were black, and 55% had not responded to prior HCV treatment. The overall SVR12 rate was 96% (321/335). Two patients had on-treatment virologic failure judged to be a result of nonadherence, 10 had virologic relapse after discontinuing treatment, 1 died from endocarditis associated with injection drug use, and 1 was lost to follow-up. SVR12 rates were 94% (63/67) among patients with compensated cirrhosis and 97% (179/185) among treatment-experienced patients. No patients discontinued the study drugs because of an adverse event. Although all patients had an eGFR >60 mL/min at study entry, drug interaction studies suggested that patients receiving tenofovir disoproxil fumarate could have increased tenofovir levels. There were 4 patients in whom serum creatinine level rose to ≥0.4 mg/dL. Two remained on tenofovir disoproxil fumarate, 1 had the tenofovir disoproxil fumarate dose reduced, and the other stopped taking tenofovir disoproxil fumarate.

Neither the ERADICATE nor the ION-4 study investigators reported clinically significant changes in CD4 cell counts or HIV RNA levels in the study participants. Thus, these data suggest that 12 weeks of ledipasvir/sofosbuvir is a safe and effective regimen for HIV/HCV-coinfected patients with genotype 1 infection taking selected antiretroviral therapy ([Qsinusi, 2015](#)); ([Naggie, 2015](#)). There are limited data regarding an 8-week course of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients ([Ingiliz, 2016](#)). Additionally, clinical trial data of daclatasvir (an NS5A inhibitor similar to ledipasvir) plus sofosbuvir in HIV/HCV-coinfected patients demonstrated a lower SVR rate (76%) with 8 weeks of treatment compared to 12 weeks of therapy (97%). Therefore, a shortened treatment course for HIV/HCV-coinfected persons cannot be recommended at this time.

Pharmacology and Drug Interaction Data

Drug interaction studies of ledipasvir (with or without sofosbuvir) with antiretroviral drugs in uninfected persons did not identify clinically significant interactions with abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, or rilpivirine ([German, 2014](#)); ([Gardson, 2015](#)). Interactions with maraviroc and enfuvirtide are not expected based on their pharmacologic profiles. Ledipasvir AUC is decreased by 34% when coadministered with efavirenz-containing regimens and increased by 96% when coadministered with ritonavir-boosted atazanavir ([German, 2014](#)). No dose adjustments of ledipasvir are recommended to account for these interactions.

Ledipasvir absorption is pH dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Ledipasvir/sofosbuvir increases tenofovir levels when given as tenofovir disoproxil fumarate, which may increase the risk of tenofovir-associated renal toxicity. This combination should be avoided in patients with an eGFR <60 mL/min. With the addition of ledipasvir/sofosbuvir, tenofovir levels (when given as tenofovir disoproxil fumarate) are increased with efavirenz, rilpivirine ([German, 2014](#)), dolutegravir, ritonavir-boosted atazanavir, and ritonavir-boosted darunavir ([German, 2015](#)). The absolute tenofovir levels are highest, and may exceed exposures for which there are established renal safety data, when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens. Due to lack of sufficient safety data with this drug combination, consideration should be given to changing the antiretroviral regimen. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.

In patients with an eGFR <60 mL/min who are taking tenofovir disoproxil fumarate with ledipasvir/sofosbuvir, renal parameters should be checked at baseline and at the end of treatment. Baseline parameters should include measuring creatinine level, electrolytes (including phosphorus), and urinary protein and glucose, according to recent guidelines for the management of chronic kidney disease in those with HIV, which include indications for nephrology consultation ([Lucas, 2014](#)). Changing antiretroviral therapy may be considered for those at high risk for renal toxicity—especially those with an eGFR between 30 mL/min and 60 mL/min or who have preexisting evidence of Fanconi syndrome, and particularly



Patients With HIV/HCV Coinfection

From www.HCVGuidance.org on March 19, 2018

those taking tenofovir disoproxil fumarate and a ritonavir- or cobicistat-containing regimen. Tenofovir disoproxil fumarate should also be properly dosed and adjusted for eGFR at baseline and while on therapy ([Lucas, 2014](#)).

Although there is an absence of data at this time on the renal safety of tenofovir when given as tenofovir alafenamide with ledipasvir/sofosbuvir, a study of tenofovir pharmacokinetics in healthy volunteers receiving the combination of tenofovir alafenamide, emtricitabine, and cobicistat-boosted elvitegravir with ledipasvir/sofosbuvir found that tenofovir levels were only 20% of the typical tenofovir exposures seen with tenofovir disoproxil fumarate ([Garrison, 2015](#)). Based on these pharmacokinetic data in healthy volunteers, tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients on ritonavir- or cobicistat-containing regimens.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

Paritaprevir/ritonavir/ombitasvir plus dasabuvir was approved by the FDA for use in genotype 1a and 1b infection because of its efficacy and safety in treatment-naïve patients and peginterferon/ribavirin treatment-experienced patients, with or without compensated cirrhosis. Available information about response rates with this regimen in HIV/HCV-coinfected patients comes from the first part of the phase 2 TURQUOISE-1 study. In this study, treatment-naïve (n=42) and -experienced (n=21) patients were randomly assigned to 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and weight-based ribavirin (100 mg [<75 kg] to 1200 mg [≥ 75 kg]). Of the 63 study participants, 12 had compensated cirrhosis, 56 had genotype 1a infection, and 7 had genotype 1b infection. Two study-permitted antiretroviral regimens were chosen based on pharmacokinetic data from uninfected volunteers; 35 patients entered taking tenofovir disoproxil fumarate and emtricitabine with raltegravir, and 28 patients entered taking tenofovir disoproxil fumarate and emtricitabine with ritonavir-boosted atazanavir (with the ritonavir coming from the HCV regimen during the time of coadministration). Of the 31 patients who received 12 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin, 93.5% (29/31) achieved SVR12, 1 relapsed, and 1 withdrew consent from study participation. Among the 32 patients in the 24-week arm, 90.6% (29/32) achieved SVR12, 1 experienced viral breakthrough, and 2 had apparent HCV reinfection. No treatment-related serious adverse events occurred, and no patients discontinued treatment because of medication intolerance ([Sulkowski, 2015](#)).

Pharmacology and Drug Interaction Data

Paritaprevir is an inhibitor of the hepatic uptake transporter OATP1B1. Ritonavir is coformulated with paritaprevir and ombitasvir to improve the pharmacokinetics of paritaprevir. As ritonavir has anti-HIV activity, HIV/HCV-coinfected patients should have achieved HIV RNA suppression with an ART regimen prior to initiation of this DAA therapy. Those not taking antiretroviral therapy should not receive this fixed-dose combination due to the potential for low-dose ritonavir to select for HIV protease-inhibitor resistance.

Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir are metabolized by and inhibitors of CYP enzymes (3A4 and 2C8), P-gp, BCRP, and OATP1B1. Studies of uninfected volunteers did not reveal notable pharmacologic interactions with paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus dasabuvir (250 mg), or tenofovir disoproxil fumarate and emtricitabine (when tested separately from other fixed-dose combinations), raltegravir ([Menon, 2015](#)), abacavir, lamivudine, or dolutegravir ([Khatri, 2015](#)). In uninfected volunteers, when paritaprevir/ritonavir/ombitasvir plus dasabuvir was combined with efavirenz, emtricitabine, and tenofovir disoproxil fumarate, clinically significant gastrointestinal and neurologic adverse events occurred, coincident with elevations of alanine aminotransferase levels. When paritaprevir/ritonavir/ombitasvir plus dasabuvir was combined with rilpivirine, exposures to rilpivirine were substantially increased. Therefore, rilpivirine and efavirenz should not be used with paritaprevir/ritonavir/ombitasvir plus dasabuvir.

Because ritonavir is a component of the fixed-dose combination of paritaprevir and ombitasvir, the total daily dose of ritonavir must be carefully considered when using paritaprevir/ritonavir/ombitasvir plus dasabuvir with ritonavir-boosted HIV protease inhibitors. Coadministration with ritonavir-boosted lopinavir would result in a 300 mg daily dose of ritonavir, a dose associated with substantial gastrointestinal adverse effects; this combination is not recommended. In uninfected individuals, darunavir troughs are reduced with paritaprevir/ritonavir/ombitasvir plus dasabuvir. Thus, paritaprevir/ritonavir/ombitasvir plus dasabuvir should not be used with ritonavir-boosted darunavir.



Patients With HIV/HCV Coinfection

From www.HCVGuidance.org on March 19, 2018

Paritaprevir/ritonavir/ombitasvir plus dasabuvir can be given with atazanavir but the separate ritonavir-boosting tablet should be held during paritaprevir/ritonavir/ombitasvir plus dasabuvir therapy, and atazanavir (300 mg) should be administered at the same time as the fixed-dose combination of ritonavir-boosted paritaprevir and ombitasvir. Paritaprevir levels are increased 1.5- to 3-fold with atazanavir but no dose adjustment of paritaprevir is recommended ([Khatri, 2016](#)). Inhibition of OATP1B1 by paritaprevir/ritonavir/ombitasvir plus dasabuvir increases indirect bilirubin concentrations and this effect may be attenuated in individuals taking atazanavir ([Eron, 2014](#)).

Simeprevir + Sofosbuvir

The combination of simeprevir plus sofosbuvir, with or without ribavirin, has been studied in the phase 2 COSMOS trial in patients with HCV mono-infection ([Lawitz, 2014b](#)). This study is the main basis for the recommendation supporting use of this combination for genotype 1a or 1b mono-infection. Simeprevir plus sofosbuvir has been used anecdotally in patients with HIV/HCV coinfection, with a recent report of achieving SVR in 92% (11/12) of patients ([Del Bello, 2016](#)). Despite the dearth of study data, this regimen may be considered for the treatment of genotype 1 infection in patients with HIV/HCV coinfection who are receiving an antiretroviral therapy regimen that may be coadministered with simeprevir plus sofosbuvir.

Similarly, few data exist for the combination of sofosbuvir plus simeprevir for the retreatment of HCV infection in HIV/HCV-coinfected patients. However, preliminary results obtained for HCV-mono-infected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in HIV/HCV-coinfected patients receiving compatible antiretroviral therapy (see [Retreatment](#) section) ([Lawitz, 2014b](#)).

Pharmacology and Drug Interaction Data

Simeprevir is metabolized primarily by CYP3A4 and is therefore susceptible to drug interactions with inhibitors and inducers of this enzyme. Simeprevir is also an inhibitor of OATP1B1 and P-gp. Drug interaction studies with antiretroviral drugs in HIV-uninfected volunteers suggest no substantial interactions with tenofovir, rilpivirine, dolutegravir, or raltegravir. However, simeprevir concentrations were substantially decreased when dosed with efavirenz, and substantially increased when dosed with ritonavir-boosted darunavir ([MacBrayne, 2017](#)). Use with efavirenz, etravirine, cobicistat, or boosted HIV protease inhibitors is not recommended ([Quwerkerk-Mahadevan, 2016](#)).

Sofosbuvir/Velpatasvir

The safety and efficacy of 12 weeks of sofosbuvir/velpatasvir were evaluated in a phase 3 study among 106 antiretroviral-controlled, HIV/HCV-coinfected patients ([Wyles, 2016](#)). Patients with genotype 1, 2, 3, or 4 infection were included; 18% (19/106) had compensated cirrhosis. HIV was controlled on ART including non-nucleoside reverse-transcriptase inhibitor (rilpivirine), integrase inhibitor (raltegravir or elvitegravir/cobicistat), or ritonavir-boosted protease inhibitor (atazanavir, lopinavir, or darunavir) based regimens with either tenofovir/emtricitabine or abacavir/lamivudine. Fifty-three percent (56/106) of participants were on tenofovir disoproxil fumarate with a pharmacologic boosting agent (either ritonavir or cobicistat). Neither efavirenz nor etravirine were allowed in this study as concomitant dosing with sofosbuvir/velpatasvir in healthy volunteers resulted in clinically significant decreases in velpatasvir exposure. SVR12 was 95% with 2 relapses, both occurring in genotype 1a-infected patients. Similar results were noted in patients with compensated cirrhosis and in those with baseline NS5A RASs (n=12 at 15% threshold; SVR12=100%). There were no clinically significant changes in serum creatinine or eGFR, and no patients required a change in their antiretroviral therapy during the study period.

In general, few HIV/HCV-coinfected patients with compensated cirrhosis have been included in clinical trials of DAAs, and no data are available regarding HIV/HCV-coinfected patients with renal insufficiency or who have undergone solid organ transplantation. Despite a lack of data, it is highly likely that response rates are similar to those of HCV-mono-infected patients, as no study to date in the DAA era has showed a lower efficacy for HIV/HCV-coinfected patients. Therefore, the respective guidance from these sections should be followed if treatment is otherwise warranted, with consideration of drug interactions.



Patients With HIV/HCV Coinfection
From www.HCVGuidance.org on March 19, 2018

Pharmacology and Drug Interaction Data

Velpatasvir is available only in a fixed-dose combination tablet with sofosbuvir. Velpatasvir is metabolized by CYP3A4, CYP2C8, and CYP2B6. It does not appear to inhibit or induce any CYP enzymes. Velpatasvir is a substrate for P-gp and BCRP, and inhibits P-gp, BCRP, and OATP1B1/1B3 but does not induce any transporters.

Velpatasvir absorption is pH dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug interaction studies with sofosbuvir/velpatasvir have been performed in HIV and HCV seronegative volunteers. As with ledipasvir/sofosbuvir, tenofovir exposures are increased, which may be problematic for individuals with an eGFR <60 mL/min or in those receiving ritonavir- or cobicistat-containing antiretroviral therapy with tenofovir disoproxil fumarate. Fifty-six HIV/HCV-coinfecting individuals receiving the combination of tenofovir disoproxil fumarate with ritonavir- or cobicistat-containing antiretroviral therapy were treated with sofosbuvir/velpatasvir in the ASTRAL-5 study with no difference in median creatinine clearance before and after sofosbuvir/velpatasvir treatment (but poor renal function was an exclusion for this study) (Wyles, 2017b). In individuals with an eGFR <60 mL/min, consider use of tenofovir alafenamide in place of tenofovir disoproxil fumarate in those requiring ritonavir- or cobicistat-containing antiretroviral therapy. If the combination of tenofovir disoproxil fumarate with a ritonavir- or cobicistat-containing antiretroviral therapy is required in patients with an eGFR <60 mL/min, renal parameters should be checked at baseline and regularly thereafter while on sofosbuvir/velpatasvir.

Velpatasvir exposures are significantly reduced with efavirenz and this combination is not recommended. Etravirine has not been studied with sofosbuvir/velpatasvir and is also not recommended. Indirect bilirubin level increases have been reported when sofosbuvir/velpatasvir was used in patients on atazanavir/ritonavir. These changes are not considered clinically significant.

Based on data from healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide relative to tenofovir disoproxil fumarate. Thus, tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy. However, there are no safety data for this combination in HIV/HCV-coinfecting patients.

Sofosbuvir/Velpatasvir/Voxilaprevir

The data supporting use of sofosbuvir/velpatasvir/voxilaprevir are described in the Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections of the guidance. This regimen has not been studied in HIV/HCV-coinfecting patients. Despite a lack of data, it is highly likely that response rates in HIV/HCV-coinfecting patients will be similar to those of HCV-monoinfecting patients, as no study to date in the DAA era has shown a lower efficacy for HIV/HCV-coinfecting patients. Therefore, the respective guidance from the aforementioned treatment and retreatment sections of the guidance should be followed, with consideration of drug-drug interactions.

Pharmacology and Drug Interaction Data

Voxilaprevir is a substrate for P-gp, OATP, BCRP, CYP3A, CYP1A2, and CYP2C8. Voxilaprevir inhibits OATP, P-gp, and BCRP. Voxilaprevir AUC is increased 331% with ritonavir-boosted atazanavir and this combination is not recommended (Garrison, 2017). Voxilaprevir AUC is increased 171% with tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat, and 143% with tenofovir disoproxil fumarate/emtricitabine and ritonavir-boosted darunavir. Although these increases in voxilaprevir AUC were not deemed clinically relevant by the manufacturer or the FDA, due to lack of clinical safety data, close monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfecting patients. Consider liver enzyme testing every 4 weeks.

Tenofovir concentrations are increased with sofosbuvir/velpatasvir/voxilaprevir when given as tenofovir disoproxil fumarate (Garrison, 2017). In individuals with an eGFR <60 mL/min, consider use of tenofovir alafenamide in place of

**Patients With HIV/HCV Coinfection**

From www.HCVGuidance.org on March 19, 2018

tenofovir disoproxil fumarate in those requiring ritonavir- or cobicistat-containing antiretroviral therapy. No substantial interactions were observed with dolutegravir, emtricitabine, raltegravir, or rilpivirine.

Velpatasvir absorption is pH dependent. Velpatasvir AUC is reduced approximately 50% when given with omeprazole 20 mg daily as part of the fixed-dose sofosbuvir/velpatasvir/voxilaprevir combination. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Table 1.**Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Preferred Regimens**

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and pink indicates the combination should be avoided.

	Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Ritonavir- boosted atazanavir (ATZ)	▲ LDV ▲ ATZ ^a	▲ VEL ▲ ATZ ^a	▲ ELB ▲ GRZ ▲ ATZ	ND	▲ ATZ
Ritonavir- boosted darunavir (DRV)	▲ LDV ◄► DRV ^a	◄► VEL ◄► DRV ^a	▲ ELB ▲ GRZ ◄► DRV	ND	▲ VOX ◄► DRV
Ritonavir- boosted lopinavir (LPV)	ND ^a	◄► VEL ◄► LPV ^a	▲ ELB ▲ GRZ ◄► LPV	ND	ND
Ritonavir- boosted tipranavir (TPV/r)	ND	ND	ND	ND	ND
Efavirenz (EFV)	▼ LDV ▼ EFV ^a	▼ VEL ▼ EFV	▼ ELB ▼ GRZ ▼ EFV	ND	ND
Rilpivirine (RPV)	◄► LDV ◄► RPV	◄► VEL ◄► RPV	◄► ELB ◄► GRZ ◄► RPV	◄► GLE ◄► PIB ▲ RPV	◄► VEL ◄► VOX ◄► RPV
Etravirine (ETV)	ND	ND	ND	ND	ND
Raltegravir (RAL)	◄► LDV ◄► RAL	◄► VEL ◄► RAL	◄► ELB ◄► GRZ ▲ RAL	◄► GLE ◄► PIB ▲ RAL	ND
Cobicistat- boosted elvitegravir (COB)	▲ LDV ▲ COB ^a	▲ VEL ▲ COB ^a	▲ ELB ▲ GRZ ▲ COB	▲ GLE ▲ PIB ▲ COB	▲ VOX ▲ COB ^a


Patients With HIV/HCV Coinfection

From www.HCVGuidance.org on March 19, 2018

	Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Dolutegravir (DTG)	◄► LDV ◄► DTG	◄► VEL ◄► DTG	◄► ELB ◄► GRZ ▲ DTG	▼ GLE ▼ PIB ▲ DTG	ND
Maraviroc (MVC)	ND	ND	ND	ND	ND
Tenofovir (TFV) disoproxil fumarate	◄► LDV ▲ TFV ^c	◄► VEL ▲ TFV	◄► ELB ◄► GRZ ▲ TFV	ND	▲ TFV ^b
Tenofovir (TFV) alafenamide	◄► LDV ▲ TFV ^d	◄► VEL ▲ TFV ^d	ND	◄► GLE ◄► PIB ◄► TFV	▲ TFV ^b

ND, No data

^a Caution only with tenofovir disoproxil fumarate

^b Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.

^c Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens.

^d Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

Table 2.
Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Alternative Regimens

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and pink indicates the combination should be avoided.

	Simeprevir/ Sofosbuvir (SMV/SOF)	Daclatasvir/ Sofosbuvir (DCV/SOF)	Paritaprevir/ Ritonavir/ Ombitasvir + Dasabuvir (ProD)	Paritaprevir/ Ritonavir/ Ombitasvir (Pro)
Ritonavir- boosted atazanavir (ATZ)	ND	▲ DCV ^a	▲ PRV ▲ ATZ	▲ PRV ◄► ATZ
Ritonavir- boosted darunavir (DRV)	▲ SMV ◄► DRV	▲ DCV ◄► DRV	▼▲ PRV ▼ DRV	▲ PRV ◄► DRV
Ritonavir- boosted lopinavir (LPV)	ND	▲ DCV ◄► LPV	▲ PRV ◄► LPV	▲ PRV ◄► LPV



Patients With HIV/HCV Coinfection

From www.HCVGuidance.org on March 19, 2018

	Simeprevir/ Sofosbuvir (SMV/SOF)	Daclatasvir/ Sofosbuvir (DCV/SOF)	Paritaprevir/ Ritonavir/ Ombitasvir + Dasabuvir (PrOD)	Paritaprevir/ Ritonavir/ Ombitasvir (PrO)
Ritonavir- boosted tipranavir (TPV/r)	ND	ND	ND	ND
Efavirenz (EFV)	▼ SMV ◄► EFV	▼ DCV ^b	NPD ^c	ND
Rilpivirine (RPV)	◄► SMV ◄► RPV	ND	▲ PRV ▲ RPV	ND
Etravirine (ETV)	ND	▼ DCV ^b	ND	ND
Raltegravir (RAL)	◄► SMV ◄► RAL	ND	◄► PrOD ▲ RAL	◄► PrO ▲ RAL
Cobicistat- boosted elvitegravir (COB)	ND	▲ DCV ^a	ND	ND
Dolutegravir (DTG)	◄► SMV ◄► DTG	◄► DCV ▲ DTG	▼ PRV ▲ DTG	ND
Maraviroc (MVC)	ND	ND	ND	ND
Tenofovir (TFV) disoproxil fumarate	◄► SMV ◄► TFV	◄► DCV ◄► TFV	◄► PrOD ◄► TFV	◄► PrO ◄► TFV
Tenofovir (TFV) alafenamide	ND	ND	ND	ND
ND, No data ^a Daclatasvir dose should be reduced to 30 mg. ^b Daclatasvir dose should be increased to 90 mg.				



Patients With HIV/HCV Coinfection
From www.HCVGuidance.org on March 19, 2018

Ribavirin

Ribavirin has the potential for dangerous drug interactions with didanosine, resulting in mitochondrial toxicity with hepatomegaly and steatosis, pancreatitis, and lactic acidosis. Thus, concomitant administration of these 2 drugs is contraindicated (Fleischer, 2004). The combined use of ribavirin and zidovudine has been reported to increase the rates of anemia and the need for ribavirin dose reduction. Thus, zidovudine is not recommended for use with ribavirin (Alvarez, 2006).

Treatment Recommendations for Patients With HIV/HCV Coinfection	
RECOMMENDED	RATING
HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).	I, B
Daily daclatasvir (refer to information above for dose) plus sofosbuvir (400 mg), with or without ribavirin, is a recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals. Refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for treatment duration.	I, B

Regimens Not Recommended for Patients With HIV/HCV Coinfection	
NOT RECOMMENDED	RATING
Ledipasvir/sofosbuvir for 8 weeks is not recommended, regardless of baseline HCV RNA level.	IIb, C

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration of treatment is unclear, expert consultation should be sought.

Last update: September 21, 2017



Patients With Decompensated Cirrhosis
From www.HCVGuidance.org on March 19, 2018

Patients With Decompensated Cirrhosis

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis ¹	
RECOMMENDED	RATING ²
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12, including patients with CTP class C cirrhosis ([Manns, 2016](#)); ([Curry, 2015](#)); ([Charlton, 2015](#)); ([Welzel, 2016](#)). However, improvements may be insufficient to avoid liver-related death or the need for liver transplantation ([Belli, 2016](#)), highlighting that not everyone benefits from DAA therapy ([Fernandez-Carrillo, 2016](#)). Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified, though patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than treatment ([Terraault, 2017](#)); ([Belli, 2016](#)).

Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotics without HCC ([Prenner, 2017](#)); ([Beste, 2017](#)). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (with and without ribavirin), overall SVR rates were 91% in patients without HCC vs 74% in those with HCC ([Beste, 2017](#)). After adjusting for confounders, the presence of HCC was associated with a lower likelihood of SVR (AOR=0.38). Whether this lower rate of SVR can be overcome with an extended duration of therapy is unknown.


Patients With Decompensated Cirrhosis

From www.HCVGuidance.org on March 19, 2018

Decompensated Cirrhosis Genotype 1, 4, 5, or 6 Infection

Recommended regimens listed by evidence level and alphabetically for:		
Patients With Decompensated Cirrhosis^a Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Eligible		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, A ^b
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin ^c	12 weeks	I, A ^d
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg) ^e plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B
^a Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. ^b Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis. ^c Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated. ^d Only available data for genotype 6 are in patients with compensated cirrhosis. ^e The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.		

Recommended regimens listed by evidence level and alphabetically for:		
Patients With Decompensated Cirrhosis^a Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Ineligible		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A ^b
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A ^c
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg) ^d plus sofosbuvir (400 mg)	24 weeks	II, C
^a Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. ^b Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis. ^c Only available data for genotype 6 are in patients with compensated cirrhosis. ^d The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.		



Patients With Decompensated Cirrhosis
From www.HCVGuidance.org on March 19, 2018

Recommended regimens listed by evidence level and alphabetically for:

**Patients With Decompensated Cirrhosis^a and Genotype 1, 4, 5, or 6 Infection
in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed**

RECOMMENDED	DURATION	RATING ^①
Prior sofosbuvir-based treatment failure only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated)	24 weeks	II, C ^b
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin ^c	24 weeks	II, C ^d

^a Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

^b Only available data for genotype 6 are in patients with compensated cirrhosis.

^c Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis.

^d Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.

Ledipasvir/Sofosbuvir

The US-based, multicenter, randomized, open-label, phase 2 SOLAR-1 trial included 108 patients with genotype 1 or 4 infection and decompensated cirrhosis; 59 were categorized as CTP class B (score 7 to 9) and 49 were categorized as CTP class C (score 10 to 12). Participants were randomly assigned to 12 weeks or 24 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated) (Charlton, 2015b). After excluding the 7 patients who underwent liver transplantation during the study, the SVR rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in those who received 24 weeks of treatment. Similarly, the SVR rates were 86% and 87%, respectively, with 12 weeks and 24 weeks of antiviral therapy in the CTP class C patients. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively.

In the majority of participants with CTP class B or C disease, the MELD and CTP scores decreased between baseline and post-treatment week 4. As expected, the frequency of serious adverse events increased with treatment duration in both the CTP class B group (10% week 12; 34% week 24) and the CTP class C group (26% week 12; 42% week 24). Most of the serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the patients with decompensated cirrhosis was 600 mg. Therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients in the 24-week treatment arm.

The multicenter (Europe, Canada, Australia, and New Zealand), randomized, open-label, phase 2 SOLAR-2 study included 160 genotype 1- or 4-infected patients with decompensated cirrhosis (CTP class B or C). Study participants, who were treatment-naïve or -experienced, were randomly assigned to 12 weeks or 24 weeks of daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated). All participants had a hemoglobin level >10 g/dL and an estimated glomerular filtration rate (eGFR) >40 mL/min (Manns, 2016). Among the 150 patients with decompensated cirrhosis who completed therapy and had evaluable efficacy results, SVR12 was achieved in 85% (61/72) of those in the 12-week study arm (90% [43/48] CTP class B; 75% [18/24] CTP class C). SVR 12 was achieved by 90% (70/78) of patients with decompensated cirrhosis in the 24-week study (98% [47/48] CTP class B; 77% [23/30] CTP class C). Post-therapy virologic relapse occurred in 6% (9/150) of the patients with decompensated cirrhosis who completed therapy (7 in 12-week arm; 2 in 24-week arm).

Baseline CTP and MELD scores improved in the majority of the treated patients, but some participants experienced



Patients With Decompensated Cirrhosis
From www.HCVGuidance.org on March 19, 2018

worsening hepatic function. Among nontransplanted patients whose MELD score was ≥ 15 at baseline, 80% (20/25) had a MELD score < 15 at SVR12. Among those with a MELD score < 15 at baseline, 4% (2/56) had a MELD score ≥ 15 at SVR12. During the study, 8% (13/160) of the enrolled patients with decompensated cirrhosis (2 CTP class B, 11 CTP class C) died from various causes but none of the deaths were attributed to antiviral therapy. Serious adverse events occurred in approximately 28% of patients with decompensated cirrhosis with no significant difference between the 12-week and 24-week treatment arms.

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared to daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks (with a 12-week placebo phase). Study participants included 154 patients with compensated cirrhosis and genotype 1 infection in whom prior peginterferon/ribavirin treatment failed (for most patients, treatment with peginterferon/ribavirin plus a protease inhibitor also failed) (Bourliere, 2015). The mean MELD score was 7 (range, 6 to 16), 26% of patients had varices, and 13% had low serum albumin levels. The SVR12 rate was 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache, and pruritus; the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Collectively, these results indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis and genotype 1 or 4 infection. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients received a ribavirin dose of 600 mg/d. Of 17 patients (16 genotype 1; 1 genotype 4) in the SOLAR-1 and SOLAR-2 trials (6 CPT class B; 11 CPT class C) who received ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks prior to or up to the time of liver transplant, all had HCV RNA < 15 IU/mL at the time of transplantation. Sixteen of the 17 patients achieved post-transplant SVR12; 1 patient died at post-op day 15, but the HCV RNA was < 15 IU/mL on day 14 (Yoshida, 2017).

Real-world cohort studies have reported SVR rates in patients with decompensated cirrhosis. Foster and colleagues reported on the use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg)/sofosbuvir (400 mg), with or without ribavirin, for 12 weeks in 235 genotype 1-infected patients from the United Kingdom (Foster, 2016). The SVR rates were similar in the 235 genotype participants receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% and 81%, respectively). In this observational cohort study, 91% of the patients received ribavirin; only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the patients had a serious adverse event; none were treatment related.

The multicenter, prospective, observational HCV-TARGET study examined the real-world efficacy of ledipasvir/sofosbuvir (with or without ribavirin) for various treatment durations. The SVR12 rate among genotype 1 patients with a history of clinically decompensated cirrhosis was 90% (263/293) among evaluable patients (Terrault, 2016). In this cohort, 29% of patients with decompensated cirrhosis were treated with ribavirin and 48% received 24 weeks treatment.

A phase 2a, open-label study of 14 patients with compensated cirrhosis and genotype 1 infection in whom prior sofosbuvir-based therapy failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate (Qsinusi, 2014). In addition, results of an open-label, phase 2 study of 51 genotype 1-infected patients in whom prior sofosbuvir-based therapy failed demonstrated that a 12-week course of ledipasvir/sofosbuvir plus weight-based ribavirin (1000 mg/d to 1200 mg/d) led to an overall SVR12 rate of 98%, including 100% (14/14) among those patients with compensated cirrhosis (Wyles, 2015b).

Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Notably, 10% of patients were CTP class A or class C at treatment baseline. Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight < 75 kg; 1200 mg/d, weight ≥ 75 kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype. All participants had a hemoglobin level > 10 g/dL.



Patients With Decompensated Cirrhosis
From www.HCVGuidance.org on March 19, 2018

and an eGFR ≥ 50 mL/min (Curry, 2015b). The genotype/subtype distribution of the participants was 60% (159/267) genotype 1a; 18% (48/267) genotype 1b; 4% (12/267) genotype 2; 15% (39/267) genotype 3; 3% (8/267) genotype 4; and <1% (1/267) genotype 6. Ninety-five percent of patients had a baseline MELD score ≤ 15 .

The SVR rates were 83% among those in the 12-week sofosbuvir/velpatasvir study arm, 94% in the 12-week sofosbuvir/velpatasvir plus ribavirin arm, and 86% in the 24-week sofosbuvir/velpatasvir arm. Among patients with genotype 1 infection, the SVR rates were 88%, 96%, and 92%, respectively. Twenty-two participants had virologic failure, including 20 patients with relapse and 2 patients (genotype 3) with on-treatment virologic breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virologic relapse.

At post-treatment week 12, 47% of patients had an improvement in CTP score, 42% had no change, and 11% had an increased CTP score. Nine patients (3%) died due to various causes during the study; no deaths were judged to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia (ie, hemoglobin <10 g/dL) was reported in 23% of the group receiving ribavirin, and 8% and 9% in those who received 12 weeks and 24 weeks of sofosbuvir/velpatasvir without ribavirin, respectively.

A phase 2, open-label, single-arm study conducted by Gane and colleagues evaluated a 24-week course of sofosbuvir/velpatasvir plus weight-based ribavirin among 65 patients with a history of treatment failure with an NS5A-containing regimen (Gane, 2016). Twenty-six percent of enrolled patients had compensated cirrhosis. The overall SVR12 rate was 91% (59/65), including 97% (33/34) among genotype 1-infected patients, 91% (13/14) in those with genotype 2 infection, and 76% (13/17) in patients with genotype 3. To date, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

The phase 3, multicenter ASTRAL-1 trial evaluated the efficacy and safety of a 12-week course of daily fixed-dose sofosbuvir/velpatasvir among treatment-naïve and experienced patients with genotype 1, 2, 4, 5, or 6 infection. The study included 35 patients with genotype 5 infection and 41 patients with genotype 6 infection (Feld, 2015). The overall SVR12 rates were 97% (34/35) in genotype 5-infected patients and 100% (41/41) in those with genotype 6 infection. Of note, 100% SVR12 was achieved in the small number of genotype 5 patients (n=5) and genotype 6 patients (n=6) with compensated cirrhosis enrolled in ASTRAL-1.

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-1 trial evaluated the efficacy and safety of 12 weeks of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin (600 mg with possible escalation to 1000 mg as tolerated) among patients with cirrhosis (CTP class A, B, or C; n=60) or HCV recurrence after liver transplantation (n=53). Treatment-naïve and -experienced patients were enrolled. More than 75% of participants had genotype 1 infection, although patients with genotype 2, 3, or 4 infection were also represented in the cirrhosis cohort. The CTP breakdown was 20% (12/60) class A, 53% (32/60) class B, and 26% (16/60) class C.

The SVR12 rates were 83% (50/60) among those in the cirrhosis group and 94% (50/53) among those with recurrent HCV infection post liver transplant. In the population with cirrhosis, SVR12 rates by genotype were: 82% (37/45) genotype 1; 80% (4/5) genotype 2; 83% (5/6) genotype 3; and 100% (4/4) genotype 4. Response rates differed based on severity of cirrhosis; SVR12 rates were 92% (11/12) among those with CTP class A cirrhosis, 94% (30/32) among those with class B, and 56% (9/16) in patients with class C cirrhosis (Poordad, 2016).

An observational cohort study from the United Kingdom conducted by Foster and colleagues examined various combinations of DAA agents in patients with decompensated cirrhosis (CTP score ≥ 7), recurrent HCV after liver transplantation, or a severe extrahepatic manifestation of HCV disease. The study treatment regimens included a 12-week course of daclatasvir plus sofosbuvir, with or without ribavirin. Among the 200 genotype 1-infected patients with decompensated cirrhosis enrolled in the study, the SVR12 for 12 weeks of daclatasvir/sofosbuvir plus ribavirin was 88% (30/34). SVR12 for daclatasvir/sofosbuvir without ribavirin was 50%, but only 4 patients received this regimen (Foster, 2016).

Overall SVR12 rates were similar in the genotype 1-infected participants receiving ledipasvir/sofosbuvir plus ribavirin or



Patients With Decompensated Cirrhosis

From www.HCVGuidance.org on March 19, 2018

ledipasvir/sofosbuvir (86% and 81%, respectively) and those receiving daclatasvir/sofosbuvir with ribavirin or daclatasvir/sofosbuvir therapy (82% and 60%, respectively). In this real-world study, 91% of the patients received ribavirin; only 6% discontinued ribavirin but 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the participants had a serious adverse event; none were treatment related. These data highlight the lower efficacy and increased safety concerns when treating patients with more advanced liver failure.

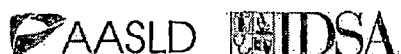
Protease-Inhibitor Containing Regimens

To date, the fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) has not been rigorously studied in patients with decompensated cirrhosis. A phase 2, nonrandomized, open-label study of elbasvir/grazoprevir for 12 weeks was completed in 30 genotype 1-infected patients with CTP class B cirrhosis (Jacobson, 2015). The SVR12 rate was 90% (27/30); 1 patient died of liver failure at post-treatment week 4 and 2 patients relapsed. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. However, there are no safety or efficacy data regarding the US Food and Drug Administration (FDA)-approved elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Recent data reported by the FDA have demonstrated that some patients with compensated cirrhosis treated with paritaprevir/ritonavir/ombitasvir \pm dasabuvir may develop rapid-onset direct hyperbilirubinemia without ALT elevation within 1 to 4 weeks of starting treatment, which can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received paritaprevir/ritonavir/ombitasvir plus dasabuvir developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, paritaprevir/ritonavir/ombitasvir \pm dasabuvir is contraindicated in all patients with decompensated cirrhosis due to concerns about hepatotoxicity. In addition, all patients with compensated cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks while on therapy.

The daily fixed dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has not been studied in patients with decompensated cirrhosis and, pending additional safety data, is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) has not been studied in patients with hepatic decompensation. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CTP class B or C) until further data are available.



Patients With Decompensated Cirrhosis
From www.HCVGuidance.org on March 19, 2018

Decompensated Cirrhosis Genotype 2 or 3 Infection

Recommended Regimens listed by evidence level and alphabetically for: Patients With Decompensated Cirrhosis^a Who Have Genotype 2 or 3 Infection and Are Ribavirin Eligible		
RECOMMENDED	DURATION	RATING [Ⓢ]
Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, B
^a Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. ^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.		

Recommended regimens listed by evidence level and alphabetically for: Patients With Decompensated Cirrhosis^a Who Have Genotype 2 or 3 Infection and Are Ribavirin Ineligible		
RECOMMENDED	DURATION	RATING [Ⓢ]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A
Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg)	24 weeks	II, C
^a Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. ^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.		



Patients With Decompensated Cirrhosis
From www.HCVGuidance.org on March 19, 2018

Recommended regimens listed by evidence level and alphabetically for Patients With Decompensated Cirrhosis and Genotype 2 or 3 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin ^b	24 weeks	II, C
^a Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. ^b Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.		

Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight <75 kg; 1200 mg/d, weight ≥75 kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype.

The SVR rates among the 12 patients with CTP class B cirrhosis and genotype 2 infection were 100% (8/8) with sofosbuvir/velpatasvir for 12 weeks (with or without ribavirin), and 75% (3/4) with sofosbuvir/velpatasvir for 24 weeks. Among 39 patients with CTP class B cirrhosis with genotype 3 infection, the SVR rates were 50% (7/14) for 12 weeks of sofosbuvir/velpatasvir without ribavirin, 85% (11/13) for 12 weeks of sofosbuvir/velpatasvir plus ribavirin, and 50% (6/12) for 24 weeks of sofosbuvir/velpatasvir. Therefore, genotype 3-infected patients in particular appear to benefit from the addition of ribavirin to the regimen (Curry, 2015b). For patients with decompensated cirrhosis who are ribavirin ineligible, sofosbuvir/velpatasvir for 24 weeks is currently recommended, but additional studies involving larger numbers of patients are needed to define the optimal duration of therapy.

Sofosbuvir/velpatasvir has not been studied in CTP class C patients. There are no data on the outcomes of patients with decompensated cirrhosis and a history of prior sofosbuvir plus NS5A failure. However, among 69 patients (28% with compensated cirrhosis) with prior NS5A failure treated with sofosbuvir/velpatasvir plus ribavirin for 24 weeks, the SVR rates were 97% for genotype 1 (83% with compensated cirrhosis), 93% (13/14) for genotype 2 (no patients with cirrhosis), and 78% (75% with compensated cirrhosis) for genotype 3 (Gane, 2017).

Daclatasvir + Sofosbuvir

Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without and with cirrhosis. Although daclatasvir/sofosbuvir was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC₅₀) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In clinical trials, daclatasvir/sofosbuvir was associated with high SVR rates in treatment-naïve patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment to 24 weeks. For patients with genotype 2 infection who require treatment but cannot tolerate ribavirin, an alternative regimen of daclatasvir/sofosbuvir for 12 weeks is



Patients With Decompensated Cirrhosis

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recommended with consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (ie, decompensated cirrhosis).

Relevant data from the ALLY-1 study support use of daclatasvir/sofosbuvir plus ribavirin in patients with genotype 2 or 3 infection who have decompensated cirrhosis. Sixty patients with predominantly (80%) decompensated cirrhosis (CPT class B/C) were treated with daclatasvir/sofosbuvir plus ribavirin (600 mg/d, increased to tolerability). SVR rates were 80% (4/5) for genotype 2 patients and 83% (5/6) for genotype 3 patients with advanced cirrhosis ([Poordad, 2016](#)).

Broader experiences with treatment of genotype 3-infected patients with decompensated cirrhosis have been reported from real-world cohort studies. In a cohort from the United Kingdom, 110 patients with decompensated cirrhosis and genotype 3 infection treated with daclatasvir/sofosbuvir with or without ribavirin (600 mg/d, increased to tolerability) demonstrated SVR12 rates of 71% (75/105) and 60% (3/5), respectively ([Foster, 2016](#)). In comparison, among 62 patients with decompensated cirrhosis and genotype 3 infection treated with ledipasvir/sofosbuvir with or without ribavirin, the SVR12 rates were 65% (37/57) and 40% (2/5), respectively. In a multicenter Spanish study of daclatasvir/sofosbuvir with or without ribavirin in 123 genotype 3-infected patients (71% receiving 24 weeks), SVR12 was 94% in both CPT class A and CPT class B/C patients ([Alonso, 2017](#)). However, compared to CPT class A patients, the CPT class B/C patients had more frequent serious adverse events (16.7% vs 3.6%) and episodes of hepatic decompensation (5.2% vs 2.3%).

Protease-Inhibitor Containing Regimens

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has activity against genotypes 2 and 3 but has not been studied in patients with decompensated cirrhosis. Pending additional safety data, this regimen is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) is effective in patients with genotypes 2 and 3 but this drug combination has not been studied in patients with decompensated cirrhosis. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CPT class B or C) until further data are available.

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen should be considered. When the correct drug combination or treatment duration is unclear, expert consultation should be sought.

**Patients With Decompensated Cirrhosis**

From www.HCVGuidance.org on March 19, 2018

Regimens not recommended for:	
Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C) ¹	
NOT RECOMMENDED	RATING ²
Paritaprevir-based regimens	III, B
Simeprevir-based regimens	III, B
Elbasvir/grazoprevir-based regimens	III, C
Glecaprevir/pibrentasvir	III, C
Sofosbuvir/velpatasvir/voxilaprevir	III, C

Interferon should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment, CTP class B or C) because of the potential for worsening hepatic decompensation. Limited data exist for the use of simeprevir in patients with CPT class B cirrhosis (Modi, 2016); (Lawitz, 2017). In a study of 40 patients (19 CPT class A, 21 CPT class B) with genotype 1 or 4 infection treated with simeprevir, sofosbuvir and daclatasvir for 12 weeks, the mean pharmacokinetic exposure to simeprevir at week 8 of therapy was 2.2-fold higher in patients with CPT class B versus CPT class A cirrhosis. (Lawitz, 2017). All patients achieved SVR12 but grade 3 or 4 bilirubin elevations were seen in 18% and 5% of patients, respectively, though none were associated with an ALT increase or the need for drug discontinuation. No data are available for use of the currently approved doses of elbasvir/grazoprevir, glecaprevir/pibrentasvir, or sofosbuvir/velpatasvir/voxilaprevir in patients with decompensated cirrhosis.

Recent data reported by the FDA have demonstrated that some patients with compensated cirrhosis treated with paritaprevir/ritonavir/ombitasvir \pm dasabuvir may develop rapid-onset direct hyperbilirubinemia without ALT elevation within 1 to 4 weeks of starting treatment, which can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received paritaprevir/ritonavir/ombitasvir plus dasabuvir developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, paritaprevir/ritonavir/ombitasvir \pm dasabuvir is contraindicated in all patients with decompensated cirrhosis due to concerns about hepatotoxicity. In addition, all patients with compensated cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks while on therapy.

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Patients Who Develop Recurrent HCV Infection Post Liver...
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Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

Post Liver Transplantation: Genotype 1, 4, 5, or 6 Infection

Recommended regimens listed by evidence level and alphabetically for: Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft Without Cirrhosis		
RECOMMENDED	DURATION	RATING ¹
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	I, A
^a This is a 3-tablet coformulation. Please refer to the prescribing information.		

Recommended regimen for: Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft With Compensated Cirrhosis ³		
RECOMMENDED	DURATION	RATING ¹
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks	12 weeks	I, A



Patients Who Develop Recurrent HCV Infection Post Liver...
From www.HCVGuidance.org on March 19, 2018

Alternative regimens listed by evidence level and alphabetically for: Treatment-Naïve and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft, With or Without Compensated Cirrhosis ¹		
ALTERNATIVE	DURATION	RATING ¹
Daily daclatasvir (60 mg) ^a plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B
Genotype 1 or 4 infection only: Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	IIa, C
^a The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy. ^b This is a 3-tablet coformulation. Please refer to the prescribing information.		

Recommended regimen for: Treatment-Naïve and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft and Decompensated Cirrhosis ^{a, 1}		
RECOMMENDED	DURATION	RATING ¹
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B
^a Includes CTP class B and class C patients.		



Patients Who Develop Recurrent HCV Infection Post Liver...
From www.HCVGuidance.org on March 19, 2018

Post Liver Transplantation: Genotype 2 or 3 Infection

Recommended regimens listed by evidence level and alphabetically for: Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft Without Cirrhosis		
RECOMMENDED	DURATION	RATING ^①
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	12 weeks	I, A
Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
^a This is a 3-tablet coformulation. Please refer to the prescribing information. ^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.		

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft With Compensated Cirrhosis ^①		
RECOMMENDED	DURATION	RATING ^①
Daily daclatasvir (60 mg) ^a plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
ALTERNATIVE	DURATION	RATING ^①
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	II, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C
^a The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy. ^b This is a 3-tablet coformulation. Please refer to the prescribing information.		



Patients Who Develop Recurrent HCV Infection Post Liver...
From www.HCVGuidance.org on March 19, 2018

Recommended regimens listed by evidence level and alphabetically for: Treatment-Naïve and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft and Decompensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING ^b
Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C

^a Includes CTP class B and class C patients.
^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

Glecaprevir/Pibrentasvir

The MAGELLAN-2 trial was an open-label, multicenter, single-arm, phase 3 study that evaluated a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in 80 liver transplant recipients and 20 kidney transplant recipients without cirrhosis. All genotypes were represented except genotype 5; 57% of participants had genotype 1 infection and 24% had genotype 3. Except for genotype 3-infected patients (all of whom were treatment naïve), treatment-experienced patients were included (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Eighty percent of patients had Metavir stage F0 or F1 fibrosis, 6% had F2, and 14% had F3. Any stable immunosuppressive regimen was allowed, except cyclosporine >100 mg/d and prednisone >10 mg/d. SVR was achieved in 98% (98/100) of patients with no virologic breakthroughs on treatment and 1 post-treatment relapse (Beau, 2017). There were no treatment discontinuations due to drug-associated adverse effects. One episode of mild rejection occurred that was assessed to be unrelated to drug interactions. This regimen offers a ribavirin-free option for noncirrhotic liver or kidney transplant recipients. Although glecaprevir/pibrentasvir has not been studied in transplant recipients with compensated cirrhosis, this regimen may be considered in patients who are ribavirin ineligible.

Ledipasvir/Sofosbuvir

The SOLAR-1 study was a large, US-based, multicenter, open-label, phase 2 trial that included 223 liver transplant recipients with genotype 1 or 4 infection whose baseline characteristics encompassed a broad spectrum of histologic and clinical severity of HCV recurrence. One hundred and eleven patients were Metavir stage F0 to F3, 51 had compensated CTP class A cirrhosis, and 61 had decompensated CTP class B or class C cirrhosis. Study participants were randomly assigned to 12 weeks or 24 weeks of a fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin. The ribavirin dose was weight based for patients without cirrhosis or with compensated cirrhosis (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]). For patients with CTP class B or class C cirrhosis, ribavirin was initiated at 600 mg/d followed by dose escalation as tolerated. Only 4% of enrolled participants discontinued treatment prematurely because of adverse events related to the study drugs (Charlton, 2015b).

On an intention-to-treat basis, SVR was achieved in 96% (53/55) and 98% (55/56) of liver transplant patients without cirrhosis in the 12- and 24-week treatment arms, respectively. Among those with compensated cirrhosis, SVR was 96% in both the 12- and 24-week treatment arms. Efficacy was lower in patients with CTP class B or class C cirrhosis post liver transplantation. Among those with CTP class B cirrhosis, SVR rates were 86% and 88% in the 12- and 24-week treatment



Patients Who Develop Recurrent HCV Infection Post Liver...
From www.HCVGuidance.org on March 19, 2018

arms, respectively. Among patients with CTP class C cirrhosis, SVR rates were 60% and 75% in the 12- and 24-week treatment arms, respectively. Mortality rate during the study was 10% among patients with CTP class B or class C cirrhosis ([Charlton, 2015b](#)).

Similar results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, Canada, and New Zealand. The study included 168 liver transplant recipients with genotype 1 or 4 infection. Among the post-transplantation patients, 101 had no cirrhosis (Metavir stage F0 to F3), 67 had CTP class A compensated cirrhosis, 45 had CTP class B cirrhosis, and 8 had CTP class C decompensation. SVR rates in post-transplantation, noncirrhotic patients were 94% (49/52) and 100% (49/49) for 12 weeks and 24 weeks of treatment, respectively. Among patients with compensated cirrhosis after transplantation, SVR was 97% (33/34; 32/33) in both the 12- and 24-week treatment arms. For patients with CTP class B cirrhosis, comparable SVR rates were 95% (21/22) and 100% (23/23), respectively. Among those with CTP class C cirrhosis, SVR rates were 33% (1/3) and 80% (4/5), respectively. Considering both pre- and post-transplantation patients with CTP class B or class C cirrhosis, SVR rates were 85% (61/72) and 90% (70/78) for 12 weeks and 24 weeks of treatment, respectively.

As the relative importance of ribavirin cannot be ascertained from the SOLAR studies (all patients received ribavirin), the safest presumption is that ribavirin may contribute to the high SVR rates observed.

Most clinical trials to date have focused on patients who were at least 6 months post transplantation, but there is no a priori reason not to consider earlier treatment if the patient is on stable immunosuppression and has recovered from postoperative complications. Treatment during the first 6 to 12 months post transplantation certainly seems reasonable to reduce the likelihood of treating patients with more advanced liver disease. A phase 2 study of prophylactic ledipasvir/sofosbuvir enrolled 16 genotype 1-infected liver transplant recipients (most with hepatocellular carcinoma as the indication). Treatment was initiated immediately preoperatively and continued for 4 weeks post transplantation ([Levitsky, 2016](#)). SVR12 post transplantation was attained in 88% (15/16) of patients. While these results are too preliminary upon which to base recommendations, the findings provide additional data on the safety of ledipasvir/sofosbuvir early in the post-transplantation period.

An observational HCV-TARGET cohort study provides real-world data based on experience with 347 liver, 60 kidney, and 36 dual liver kidney transplant recipients. Among the enrolled patients, 86% had genotype 1 infection, 44% had cirrhosis, 26% had a history of liver decompensation, and 54% had a prior treatment failure with a non-NS5A inhibitor regimen ([Saxena, 2017](#)). Among the 279 participants treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks, the SVR rates were 97% (152/157) for those also taking ribavirin and 95% (116/122) for patients not taking ribavirin. Patients who received ribavirin were more frequently genotype 1a (versus genotype 1b), treatment experienced, and without renal dysfunction. The rate of therapy discontinuation due to an adverse event was 1.3%, highlighting the safety of the drug combination. Acute graft rejection occurred during or after cessation of therapy in 1.4% (6/415) of patients. These episodes were not judged to be a direct consequence of the antiviral regimen but serve to remind clinicians of the need to monitor immunosuppressive agent levels during direct-acting antiviral (DAA) therapy.

Another multicenter cohort of 162 patients (98% genotype 1) assessed treatment with ledipasvir/sofosbuvir (with or without ribavirin) for 8 weeks, 12 weeks, or 24 weeks. Duration of treatment and ribavirin use were provider determined. Overall SVR12 rates were 94% and 98% in those treated with ledipasvir/sofosbuvir without or with ribavirin, respectively ([Kwok, 2016](#)). SVR12 rates in patients treated for 8 weeks, 12 weeks, or 24 weeks with the ribavirin-free regimen were 86% (6/7), 94% (65/69), and 95% (39/41), respectively. SVR12 rates in the ribavirin inclusive groups were 97% (38/39) and 100% (6/6) for 12 weeks and 24 weeks of treatment, respectively.

Collectively, these real-world experiences indicate high SVR rates can be attained without inclusion of ribavirin in liver transplant patients. However, since all factors leading clinicians to include or exclude ribavirin cannot be discerned from these observational studies, inclusion of ribavirin is recommended for patients with unfavorable baseline characteristics (eg, cirrhosis, prior treatment experience) and ribavirin-free therapy is recommended for patients with a favorable baseline profile.



Patients Who Develop Recurrent HCV Infection Post Liver...
From www.HCVGuidance.org on March 19, 2018

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-1 trial evaluated the efficacy and safety of a 12-week course of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin (600 mg with possible escalation to 1000 mg as tolerated) among 60 patients with cirrhosis (CTP class A, B, or C) and 53 patients with HCV recurrence after liver transplantation. Treatment-naïve and -experienced patients were enrolled. Seventy-six percent (86/113) of participants had genotype 1 infection, including 77% (41/53) in the post-transplantation group. Eleven patients with genotype 3 infection and 1 patient with genotype 6 infection were also included in the post-transplantation group. The SVR12 rate was 94% (50/53) among those with recurrent HCV infection post transplantation. Among patients with genotype 3 infection, SVR12 rates were 83% (5/6) and 91% (10/11), respectively, in those with advanced cirrhosis and recurrent HCV infection post transplantation ([Poordad, 2016](#)).

Fontana and colleagues reported on the use of daclatasvir-containing regimens with sofosbuvir (n=77), simeprevir (n=18), or both (n=2) for 24 weeks in 97 liver transplant recipients with severe recurrent HCV infection ([Fontana, 2016](#)). Thirty-five percent of the cohort received ribavirin. Ninety-three percent of patients had genotype 1 infection, 31% had biopsy-proven cirrhosis, and 37% had severe cholestatic HCV. The proportion of patients with CTP class A, B, or C cirrhosis was 51%, 31%, and 12%, respectively. The mean MELD score was 13.0 ± 6.0 . The overall SVR12 rate was 87% (84/97). SVR12 rates were 91% (70/77) in the daclatasvir/sofosbuvir \pm ribavirin group and 72% (13/18) in the daclatasvir/simeprevir \pm ribavirin group. Although 8 patients died during or after therapy from graft dysfunction, CTP and MELD scores were stable or improved in 87% and 83% of patients, respectively. Three virologic breakthroughs and 2 relapses occurred in patients treated with daclatasvir/simeprevir. These data are consistent with findings from Herzer and colleagues who described 6 liver transplant recipients with recurrent genotype 1 infection, 4 (67%) of whom achieved SVR with a regimen of daclatasvir/simeprevir plus ribavirin ([Herzer, 2015](#)).

These data along with those from other studies suggest that daclatasvir should preferentially be combined with sofosbuvir rather than simeprevir in liver transplant recipients, particularly among patients with advanced liver disease ([EASL, 2017](#)). Daclatasvir-containing regimens appear to be well tolerated overall, with anemia noted when ribavirin is used. Cyclosporine and tacrolimus increase daclatasvir area under the curve (AUC) by 40% and 5%, respectively; these changes are not clinically significant. Daclatasvir does not cause clinically meaningful changes in calcineurin inhibitor, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels.

Simeprevir + Sofosbuvir

The prospective, randomized, phase 2 GALAXY study assessed the use of simeprevir (150 mg) plus sofosbuvir (400 mg), with or without weight-based ribavirin, for 12 weeks or 24 weeks in 46 liver transplant recipients (44 noncirrhotic) with recurrent genotype 1 infection ([O'Leary, 2017](#)). Among the randomized participants, the SVR12 rates were 100% with simeprevir plus sofosbuvir for 12 weeks, 82% with simeprevir plus sofosbuvir and ribavirin for 12 weeks, and 94% with simeprevir plus sofosbuvir for 24 weeks.

A retrospective multicenter analysis evaluated the efficacy and safety of simeprevir plus sofosbuvir, with or without ribavirin, among 123 liver transplant recipients with recurrent genotype 1 infection. Twenty percent of patients received ribavirin (at the discretion of the treating physician). Excluding 2 patients with nonvirologic failure, the SVR4 and SVR12 rates by modified intention-to-treat analysis were 92% and 91%, respectively ([Pungpapong, 2015](#)).

Another retrospective study from 21 HCV-TARGET centers reported on the efficacy of simeprevir plus sofosbuvir (79%; n=119) or simeprevir plus sofosbuvir and ribavirin (21%; n=32) among 151 liver transplant recipients with recurrent genotype 1 infection ([Brown, 2016](#)). Duration of therapy was 12 weeks for most patients; 10% (15/151) of participants received 24 weeks of treatment. Allograft cirrhosis had developed in 64% (97/151) of patients and 40% (60/151) had decompensated hepatic function. Overall SVR12 was 88% (133/151); 7% of patients experienced virologic relapse. Serious adverse events were reported in 12% of patients, and 3 deaths occurred that were unrelated to therapy.

In healthy volunteers, coadministration of a single dose of cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentration and simeprevir concentration similar to historical data ([Olysio prescribing information, 2017](#)).



Patients Who Develop Recurrent HCV Infection Post Liver...
From www.HCVGuidance.org on March 19, 2018

However, the phase 2 SATURN study reported that HCV-infected liver transplant recipients with genotype 1b infection taking simeprevir plus daclatasvir and ribavirin concomitantly with cyclosporine experienced a 5-fold increase in plasma simeprevir exposure compared with phase 3 trials of simeprevir in the absence of cyclosporine (Forns, 2017b). This interaction may be caused by cyclosporine's inhibition of organic anion transporting polypeptide 1B1 (OATP1B1), P-glycoprotein (P-gp), and cytochrome P450 3A (CYP3A). Given these findings, simeprevir should not be coadministered with cyclosporine.

Coadministration of a single dose of tacrolimus with simeprevir in healthy volunteers did not result in a notable change in tacrolimus concentration (Olysio prescribing information, 2017). An interim analysis of the SATURN study data noted an 85% increase in plasma simeprevir exposure when used concomitantly with tacrolimus compared with historical data (Forns, 2017b); (Quwerkork-Mahadevan, 2016b). Based on phase 1 studies, a 2-fold increase in simeprevir concentration is unlikely to be clinically significant. Clinicians may consider use of sofosbuvir plus simeprevir in patients receiving tacrolimus with therapeutic drug monitoring, particularly in those expected to have difficulty tolerating ribavirin (eg, patients with impaired renal function or anemia) or in patients who are unable to forgo proton pump inhibitor therapy (these agents attenuate ledipasvir absorption).

Sofosbuvir/Velpatasvir

To date, there have been no studies evaluating the safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in liver transplant recipients. For this reason, very limited recommendations on its use post liver transplantation can be made. However, with no treatment options for liver transplant recipients with genotype 2 or 3 infection who have decompensated cirrhosis, expert opinion led to the recommendation to use sofosbuvir/velpatasvir with weight-based ribavirin for these patients. Similarly, recognition of the need for alternative options for patients with genotype 2 or 3 infection and cirrhosis—especially those who are treatment experienced—led to inclusion of sofosbuvir/velpatasvir as an alternative regimen for patients with compensated cirrhosis. The safety of sofosbuvir and other NS5A inhibitors has been demonstrated and discussed above.

In the nontransplant setting (discussed in detail in the initial and retreatment sections), the phase 3, double-blind, placebo-controlled ASTRAL-1 study reported on 742 treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were randomly assigned in a 5:1 ratio to sofosbuvir/velpatasvir or placebo for 12 weeks (Feld, 2015). All patients with genotype 5 infection (n=35) received active treatment. Thirty-two percent (201/624) of patients randomized to active therapy were treatment experienced and 19% (121/624) had compensated cirrhosis (CTP class A). The genotype distribution in the active treatment arm was 34% (n=210) genotype 1a; 19% (n=118) genotype 1b; 17% (n=104) genotype 2; 19% (n=116) genotype 4; 6% (n=35) genotype 5; and 7% (n=41) genotype 6. The overall SVR was 99% (95% CI, 98 to >99). The side effect/adverse event profile of sofosbuvir/velpatasvir was similar to placebo.

In the phase 3, open-label ASTRAL-3 study, 552 treatment-naïve or -experienced patients with genotype 3 infection (with or without compensated cirrhosis) were randomized in a 1:1 ratio to 12 weeks of sofosbuvir/velpatasvir or 24 weeks of sofosbuvir plus weight-based ribavirin. The SVR12 rate was 95% (95% CI, 92 to 98) for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 rate of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 24 weeks (Foster, 2015a).

The phase 3, open-label ASTRAL-4 study enrolled 267 treatment-naïve or -experienced (55%) patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening). Patients were randomized in a 1:1:1 ratio to 12 weeks of sofosbuvir/velpatasvir, 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin, or 24 weeks of sofosbuvir/velpatasvir. SVR12 rates were 83% (75/90) for the 12-week sofosbuvir/velpatasvir regimen, 94% (82/87) for the 12-week sofosbuvir/velpatasvir plus ribavirin regimen, and 86% (77/90) for the 24-week sofosbuvir/velpatasvir regimen (Curry, 2015b). Among patients with genotype 1 infection, SVR12 rates were 88% and 96% with 12 weeks of sofosbuvir/velpatasvir without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir for 24 weeks. Virologic relapse occurred in 12% and 9% of patients in the 12-week and 24-week sofosbuvir/velpatasvir arms, respectively, compared to 2% in the 12-week sofosbuvir/velpatasvir plus ribavirin study arm. Although the ASTRAL-4 study was not powered to generate statistical significance, these results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for patients with genotype 1 or 3 infection who have decompensated cirrhosis. The participant numbers were too small for genotypes 2, 4, and 6 to differentiate the comparative efficacy of the



Patients Who Develop Recurrent HCV Infection Post Liver...
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treatment arms. Reflecting the approach in nontransplant patients with decompensated cirrhosis, liver transplant recipients with hepatic decompensation are recommended to receive sofosbuvir/velpatasvir plus ribavirin for 12 weeks.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6, a weak inhibitor of P-gp and OATP transporters, and a moderate inhibitor of the breast cancer resistance protein (BCRP) membrane transporter. As such, velpatasvir is moderately affected by potent inhibitors and, to a greater extent, potent inducers of enzyme/drug transporter systems ([Mogalian, 2016](#)). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for coadministration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus).

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or treatment duration is unclear, expert consultation should be sought.

Drug Interactions Between DAAs and Calcineurin Inhibitors

The interaction of DAA agents and calcineurin inhibitors is complex and unpredictable without formal studies of drug-drug interactions. A summary of drug interactions between calcineurin inhibitors and DAAs with recommended dosing is provided in the table below. Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a 2-fold increase in elbasvir AUC can be expected with cyclosporine coadministration. Therefore, this combination should be avoided. Since a 40% to 50% increase in tacrolimus level is predicted during coadministration with grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored.



Patients Who Develop Recurrent HCV Infection Post Liver...
 From www.HCVGuidance.org on March 19, 2018

Table. DAA Interactions With Calcineurin Inhibitors

	Cyclosporine (CSA)	Tacrolimus (TAC)
Sofosbuvir (SOF)	4.5-fold ? in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Paritaprevir / ritonavir / ombitasvir + dasabuvir (PrOD)	5.8-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir / grazoprevir (EBR/GZR)	15-fold ? in GZR AUC and 2-fold ? in EBR AUC; combination is not recommended	43% ? in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir / pibrentasvir (GLE/PIB)	5-fold ? in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses >100 mg/day	1.45-fold ? in TAC AUC; no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed
Sofosbuvir / velpatasvir / voxilaprevir (SOF/VEL/VOX)	9.4-fold ? in VOX AUC; combination is not recommended	No data; no a priori dose adjustment
AUC=area under the curve		

Last update: September 21, 2017

**Patients with Renal Impairment**

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Patients with Renal Impairment

Chronic hepatitis C is independently associated with the development of chronic kidney disease (CKD) (Rogal, 2016); (Fabrizi, 2015). A meta-analysis published in 2015 demonstrated that chronic HCV infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of CKD (Fabrizi, 2015). There is also a higher risk of progression to end-stage renal disease (ESRD) in persons with chronic HCV infection and CKD, and an increased risk of all-cause mortality in persons on dialysis (Lee, 2014); (Fabrizi, 2012).

Recommendations for Patients With CKD Stage^a 1, 2, or 3	
RECOMMENDED	RATING [ⓐ]
<p>No dose adjustment is required when using:</p> <ul style="list-style-type: none"> • Daclatasvir (60 mg)^b • Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) • Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)^c • Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) • Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) • Simeprevir (150 mg) • Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) • Sofosbuvir (400 mg) 	I, A
<p>^a Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)</p> <p>^b Refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.</p> <p>^c This is a 3-tablet coformulation. Please refer to the prescribing information.</p>	

Recommended regimens listed by evidence level and alphabetically for:			
Patients With CKD Stage^a 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)			
RECOMMENDED	GENOTYPE	DURATION	RATING [ⓐ]
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	1, 2, 3, 4, 5, 6	8 to 16 weeks ^c	I, B ^c
<p>^a Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)</p> <p>^b This is a 3-tablet coformulation. Please refer to the prescribing information.</p> <p>^c Patients in this group should be treated as would patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience (please refer to appropriate section). As such, strength of rating may be lower for certain subgroups.</p>			



Patients with Renal Impairment
From www.HCVGuidance.org on March 19, 2018

Recommended Regimens

Elbasvir/Grazoprevir

The C-SURFER trial evaluated the safety and efficacy of 12 weeks of the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) versus placebo among genotype 1-infected patients with CKD stage 4 or 5 (eGFR <30 mL/min). The initial study randomized eligible patients to immediate or deferred treatment with elbasvir/grazoprevir. The delayed treatment arm initially received placebo and was later treated with elbasvir/grazoprevir. Notably, both elbasvir and grazoprevir are primarily hepatically metabolized and undergo minimal renal elimination.

The data for the immediate treatment arm have been published ([Roth, 2015](#)). Seventy-five percent of the study participants were on hemodialysis, and 45% were African American. A small number of patients with compensated cirrhosis were included. Intention-to-treat (ITT) and modified intention-to-treat (mITT) SVR12 rates were 94% and 99%, respectively. There were no changes in erythropoietin use, hemoglobin or other adverse events in the treatment groups compared to placebo. None of the genotype 1a-infected patients with baseline NS5A resistance-associated substitutions (RASs) experienced viral relapse. The only reported relapse occurred in a patient with genotype 1b infection. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear but may relate to the moderately increased area under the curve (AUC) with grazoprevir and elbasvir observed in patients with stage 4/5 CKD ([Zepätter prescribing information, 2017](#)).

Based on these data, daily fixed-dose elbasvir/grazoprevir is recommended for the treatment of genotype 1 infection in patients with severely compromised renal function. While C-SURFER did not evaluate patients with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and 4 infection in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5. Treatment with elbasvir/grazoprevir in persons with CKD has been shown to be cost-effective in the United States ([Elbasha, 2016](#)).

Glecaprevir/Pibrentasvir

The EXPEDITION-4 trial evaluated the safety and efficacy of 12 weeks of the pangenotypic NS3/NS4A protease inhibitor glecaprevir and the pangenotypic NS5A inhibitor pibrentasvir for genotype 1, 2, 3, 4, 5, or 6 infection ([Gane, 2016b](#)). This open-label study enrolled treatment-naïve and -experienced patients (previous interferon or peginterferon ± ribavirin, or sofosbuvir and ribavirin ± peginterferon) with CKD stage 4 or 5, including hemodialysis dependence. Baseline characteristics of the 104 patients enrolled in the study were 76% male; 25% black; 19% compensated cirrhosis; 40% treatment experienced; and 82% hemodialysis dependent. The genotype distribution was 22% genotype 1a; 28% genotype 1b; 16% genotype 2; 11% genotype 3; 19% genotype 4; 1% genotype 5; and 1% genotype 6. In the study, the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120mg) was administered as three 100 mg/40 mg fixed-dose combination pills.

The study reported ITT and mITT SVR12 rates of 98% and 100%, respectively. There were no virologic failures. Two patients did not achieve SVR12; 1 patient discontinued the study due to diarrhea in the context of recent gastrointestinal bleeding and the other experienced a cerebral hemorrhage due to uncontrolled hypertension (had achieved SVR4). Adverse events included pruritus (20%), fatigue (14%), and nausea (12%). There were no serious adverse events related to the study drugs, and there were no grade 4 laboratory abnormalities reported.

The EXPEDITION-4 trial supports the efficacy and safety of glecaprevir/pibrentasvir in patients with CKD and ESRD. The recommended duration of therapy is the same as for patients without CKD.

Sofosbuvir-Based Regimens

Safe and effective doses of sofosbuvir in persons with an eGFR <30 mL/min have not been established. However, there is accumulating evidence on use of sofosbuvir-based regimens in those with an eGFR <30 mL/min ([Desnoyer, 2016](#));



Patients with Renal Impairment

From www.HCVGuidance.org on March 19, 2018

(Nazario, 2016).

The HCV-TARGET study is an ongoing prospective, observational cohort study that evaluates the use of direct-acting antiviral agents across clinical practices in North America and Europe. The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFR groups: <30 mL/min; 31-45 mL/min; 46-60 mL/min; and >60 mL/min) (Saxena, 2016). The patients received different regimens that included sofosbuvir (peginterferon/ribavirin plus sofosbuvir; simeprevir and sofosbuvir ± ribavirin; and sofosbuvir plus ribavirin). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The SVR12 rates were similar across the eGFR groups. Notably, there was progressive deterioration of renal function and related symptoms in patients with an eGFR <30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

Daclatasvir, Elbasvir, Grazoprevir, Ledipasvir, and Simeprevir

Daclatasvir, elbasvir, grazoprevir, ledipasvir, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures to many of these agents are higher in severe renal impairment—presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic metabolism—they do not require dose adjustments in the setting of renal impairment.

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or treatment duration is unclear, expert consultation should be sought.

Last update: September 21, 2017


Kidney Transplant Patients

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Kidney Transplant Patients
Genotypes 1 and 4

Recommended regimens listed by evidence level and alphabetically for:		
Treatment-Naïve and -Experienced Kidney Transplant Patients With Genotype 1 or 4 Infection, With or Without Compensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	I, A ^c IIa, C ^d
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
^a For <u>decompensated cirrhosis</u> , please refer to the appropriate section. ^b This is a 3-tablet coformulation. Please refer to the prescribing information. ^c Evidence for patients without cirrhosis ^d Evidence for patients with compensated cirrhosis		

Genotypes 2, 3, 5, and 6

Recommended and alternative regimens for:		
Treatment-Naïve and -Experienced Kidney Transplant Patients With Genotype 2, 3, 5, or 6 Infection, With or Without Compensated Cirrhosis^a		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	I, A ^c IIa, C ^d
ALTERNATIVE	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) plus low initial dose of ribavirin (600 mg; increase as tolerated)	12 weeks	II, A
^a For <u>decompensated cirrhosis</u> , please refer to the appropriate section. ^b This is a 3-tablet coformulation. Please refer to the prescribing information. ^c Genotypes 2, 3, and 6 ^d Genotype 5		



Kidney Transplant Patients

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DAA Therapy in Kidney Transplant Patients

A recent phase 2, open-label clinical trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in 114 kidney transplant recipients who were more than 6 months post transplant ([Colombo, 2017](#)). Enrolled patients had genotype 1 (91%) or 4 infection; 69% were treatment naive, and 15% had compensated cirrhosis. Patients were randomized to 12 weeks or 24 weeks of ledipasvir/sofosbuvir. Median eGFR prior to treatment was 50 mL/min for patients in the 12-week study arm and 60 mL/min for those in the 24-week arm. Overall SVR12 was 100% (114/114). Adverse events were common (64%) and serious adverse events occurred in 13 patients (11%); only 1 participant discontinued treatment because of an adverse event ([Colombo, 2017](#)). Four patients with an eGFR >40 mL/min at baseline experienced a decrease to <30 mL/min during therapy. In 3 of these patients, eGFR increased to >30 mL/min at the last visit recorded; 1 patient who had interrupted study treatment had a final value of 14.4 mL/min. All but 1 of the 6 patients with compensated cirrhosis whose eGFR decreased to <40 mL/min continued study treatment without interruption; none permanently discontinued study treatment.

Several additional reports have described successful outcomes with combination direct-acting antiviral (DAA) therapy in kidney transplant recipients ([Sawinski, 2016](#)); ([Kamar, 2016](#)); ([Saxena, 2017](#)). Sawinski and colleagues treated 20 HCV-infected kidney transplant recipients (88% genotype 1; 50% with advanced fibrosis; 60% treatment-experienced with an interferon-based regimen) with sofosbuvir-based therapy. Various regimens were used, including simeprevir plus sofosbuvir (n=9); ledipasvir/sofosbuvir (n=7); sofosbuvir plus ribavirin (n=3); and daclatasvir plus sofosbuvir (n=1). SVR12 was 100% ([Sawinski, 2016](#)). Two patients required dose reductions due to anemia (associated with ribavirin use). However, no significant changes in serum creatinine or proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on antiviral therapy ([Sawinski, 2016](#)).

Real-life data from the ongoing HCV-TARGET study have also demonstrated the efficacy of DAA therapy in patients with kidney transplant and in those with dual liver kidney transplant ([Saxena, 2017](#)). Various regimens were used, including sofosbuvir/ledipasvir ± ribavirin (85%); sofosbuvir plus daclatasvir ± ribavirin (9%); and ombitasvir/paritaprevir/ritonavir plus dasabuvir ± ribavirin (6%). The SVR12 rate was 94.6% in those with kidney transplant and 90.9% in dual liver kidney transplant recipients.

A pilot study conducted by Kamar and colleagues evaluated 25 kidney transplant recipients with chronic HCV infection who were treated with sofosbuvir-based regimens. The reported SVR12 was 100% ([Kamar, 2016](#)). Among the study participants, 76% were infected with genotype 1 and 44% had advanced fibrosis. All participants had an eGFR >30 mL/min. Treatment regimens included ledipasvir/sofosbuvir (n=9); daclatasvir plus sofosbuvir (n=4); sofosbuvir plus ribavirin (n=3); ledipasvir/sofosbuvir plus ribavirin (n=1); simeprevir and sofosbuvir plus ribavirin (n=1); simeprevir and sofosbuvir (n=6); and sofosbuvir plus peginterferon/ribavirin (n=1). Treatment was well tolerated without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels. No drug interactions with calcineurin inhibitors were observed ([Kamar, 2016](#)).

Another small study that treated 3 genotype 4-infected kidney transplant patients with sofosbuvir (400 mg) plus ribavirin (1000 mg) for 24 weeks reported 100% SVR ([Hussein, 2016](#)). Anemia was reported in 2 patients related to concomitant ribavirin use. No other adverse events were reported.

The phase 3, open-label, single arm MAGELLAN-2 study evaluated a 12-week course of the pangenotypic regimen of glecaprevir/pibrentasvir in 100 liver (n=80) and kidney (n=20) transplant recipients. SVR 12 was achieved in 99% of patients ([Reau, 2017](#)). The safety profile was excellent, and there was only 1 rejection episode in a liver transplant recipient. While this is an effective pangenotypic regimen as demonstrated in the nontransplant population, there were no genotype 5 transplant recipients in the study.

Drug interactions are an important consideration with antiviral therapy in renal transplant recipients. Please see [Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post Liver Transplantation](#) for a table of drug interactions with DAAs and calcineurin inhibitors.

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Management of Acute HCV Infection

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Management of Acute HCV Infection

This section provides guidance on the diagnosis and medical management of acute HCV infection, which is defined as presenting within 6 months of the exposure. During this period, there is a 20% to 50% chance of spontaneous resolution of the infection (Kamal, 2008). In the past, cure rates of acute infection with interferon-based treatment were very high (Grebely, 2014). The present guidance reflects current trends transitioning toward safer, interferon-sparing treatments for chronic infection and the implications for the approach to acute HCV treatment.

Acute HCV infection may result from exposure to the virus through various routes. The highest risk is associated with repeated parenteral exposure from contaminated equipment in an injection drug use setting. Lower rates of HCV transmission occur from needle-stick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low. Transmission rates among HIV-infected men who have unprotected sex with men are much higher, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood (Boesecke, 2012).

Diagnosis of Acute HCV

Recommended Testing for Diagnosing Acute HCV Infection	
RECOMMENDED	RATING
HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Testing Algorithm figure).	I, C

Recommendations for HCV testing are also found in the [HCV Testing and Linkage to Care](#) section.

Diagnosis of acute HCV infection enables estimation of annual incidence rates and transmission patterns, thereby facilitating implementation and assessment of prevention programs. At the individual level, a diagnosis of acute infection expedites linkage to care, counseling regarding high-risk behavior, and timely interventions to reduce virus transmission and liver disease progression (Bruneau, 2014). Indeed, some persons involved in high-risk behaviors practice serosorting, defined as using HCV antibody serostatus to determine whether to engage in high-risk behaviors with certain individuals (Smith, 2013). Thus, undiagnosed acutely-infected persons may be at greater risk of transmitting HCV to their presumably seronegative contacts than would be expected by chance.

The best laboratory evidence to support a diagnosis of acute HCV infection is: (1) a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative window period) (Cox, 2005), or (2) a positive HCV antibody test after a prior negative HCV antibody test (seroconversion). There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production (Chamot, 1999).

Discrete Exposure

The aforementioned types of clear, laboratory-based documentation of acute HCV infection are most easily achieved when there has been a discrete, known or suspected exposure (eg, after new onset or a change in drug injection practice, a percutaneous needle-stick exposure to an HCV-infected individual, a potentially nonsterile tattoo, or sexual assault). In those instances, baseline HCV antibody and RNA testing should be done within 48 hours of the exposure to document whether there was antecedent HCV infection (see [Testing Algorithm Figure](#)).



Management of Acute HCV Infection

From www.HCVGuidance.org on March 19, 2018

If baseline testing is negative, repeat testing is recommended. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection). If baseline HCV antibody testing is positive but RNA testing is negative, repeat HCV RNA and alanine aminotransferase (ALT) testing is recommended to identify an acute reinfection. When baseline HCV antibody and RNA testing are both positive, the person most likely already has chronic HCV infection from prior exposure(s). The frequency of repeat testing should reflect management goals. At a minimum, repeat testing should be done 4 to 6 months after baseline testing. When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 to 6 weeks for 6 months is recommended.

No Discrete Exposure

Individuals suspected of having acute HCV infection often do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult (see [Blood Test Interpretation Table](#)). Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause ([Blackard, 2008](#)); ([Kim, 2013](#)). Acute infection should also be suspected when there are low (especially $<10^4$ IU/mL) or fluctuating ($>1 \log_{10}$ IU/mL) HCV RNA values, or spontaneous clearance. These patterns do not commonly occur outside of the first 6 months after HCV infection ([McGovern, 2009](#)). A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA might also be suggestive of the early weeks of acute primary infection, although this information may need to be specifically requested from the testing laboratory ([Araujo, 2011](#)).

Patients suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, hepatitis delta virus if chronically infected with hepatitis B, and autoimmune hepatitis) ([Kushner, 2015](#)). Patients should also have HIV testing.

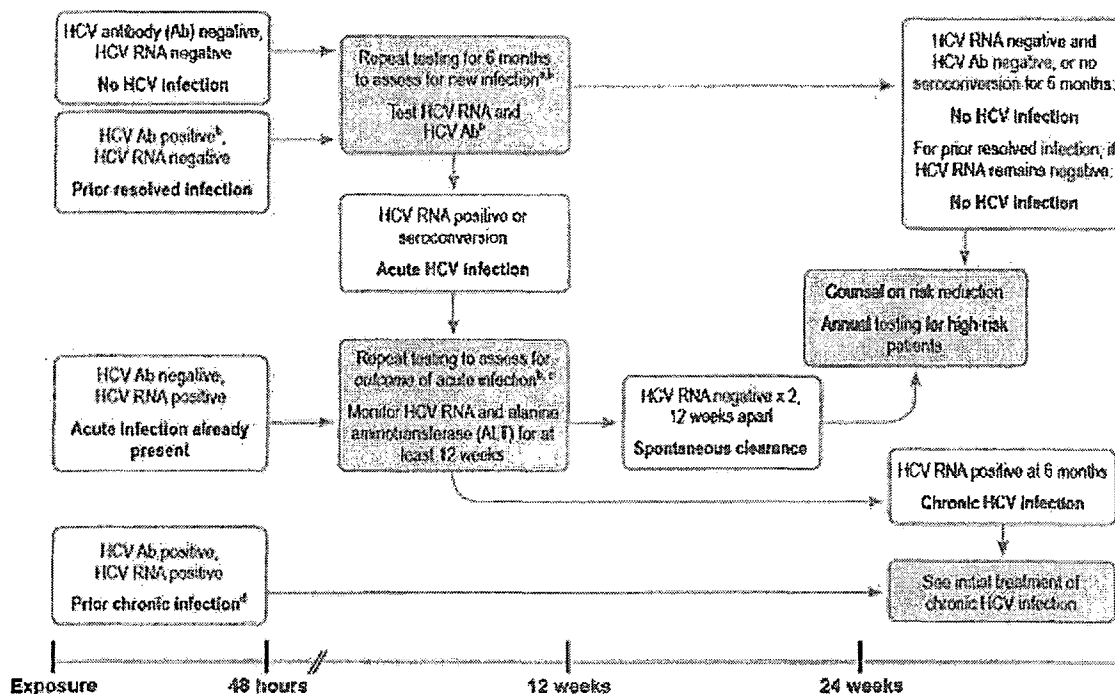
Table. Interpretation of Blood Tests for Diagnosis of Acute HCV Infection

TEST	INTERPRETATION FOR DIAGNOSIS OF ACUTE HCV
HCV Antibody	<ul style="list-style-type: none"> • Test may be negative during the first 6 weeks after exposure. • Seroconversion may be delayed or absent in immunosuppressed individuals. • Presence of HCV antibody alone does not distinguish between acute vs chronic infection. • A low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result.
HCV RNA	<ul style="list-style-type: none"> • Viral fluctuations $>1 \log_{10}$ IU/mL may indicate acute HCV infection. • HCV RNA may be transiently negative during acute HCV infection. • Presence of HCV RNA alone does not distinguish between acute vs chronic infection.
ALT	<ul style="list-style-type: none"> • Fluctuating ALT peaks suggest acute infection. • ALT may be normal during acute HCV infection. • ALT may be elevated due to other liver insults, such as alcohol consumption.



Management of Acute HCV Infection From www.HCVGuidance.org on March 19, 2018

Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure^a



- ^a Often there is no discrete exposure or the entry to health care occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be done and the diagnosis of acute infection is more challenging (see text).
- ^b Repeat HCV Ab is not needed if it is positive at baseline. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection).
- ^c Some would treat after waiting 8 weeks to 12 weeks for spontaneous clearance (see text). Benefits of HCV antiviral therapy or IFN-based (alternative) within 12 weeks of acute infection are that this may decrease transmission risk to others (eg, among injection drug users or surgeons), prevent severe complications (eg, underlying cirrhosis superinfected with acute HCV infection), and minimize chance of being lost to follow-up.
- ^d If there were additional exposures in the preceding 6 months, a patient with a new diagnosis who is HCV RNA and HCV Ab positive may still be in the acute infection phase. Symptoms, high ALT level, or viral fluctuations may help distinguish acute from chronic HCV.
- ^e Baseline testing should be done within 48 hours of exposure to determine existing infection status: HCV RNA, HCV Ab, and ALT.

Pharmacologic Prophylaxis

Pharmacologic Prophylaxis Not Recommended	
NOT RECOMMENDED	RATING
Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.	III, C



Management of Acute HCV Infection
From www.HCVGuidance.org on March 19, 2018

Although direct-acting antiviral (DAA) treatment regimens are highly efficacious and more tolerable than interferon-based therapy, there are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection. Some studies have shown that post-exposure treatment with an interferon-based regimen does not prevent infection (Nakano, 1995); (Arai, 1996).

Medical Management and Monitoring of Acute HCV Infection

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING
Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 to 8 weeks) for 6 to 12 months is also recommended to determine spontaneous clearance versus persistence of HCV infection.	I, B
Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

Patients with acute HCV infection should be counseled to reduce behaviors that could result in virus transmission, such as sharing injection equipment and engaging in high-risk sexual practices. Because the risk of transmission of other bloodborne, sexually transmitted infections (eg, HIV and HBV) is higher in the acute infection phase, some experts counsel patients with acute HCV to consider using barrier precautions, even in a stable monogamous relationship (see [HCV Testing and Linkage to Care](#)). For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

Patients with acute hepatitis C are often asymptomatic or have nonspecific symptoms (eg, fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, and/or vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of patients with acute HCV develop jaundice. Patients diagnosed with acute HCV should initially be monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of an increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). Laboratory monitoring should continue until the ALT level normalizes and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection (see [Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy](#)).

HCV infection spontaneously clears in 20% to 50% of patients (Kamal, 2008). In at least two-thirds of patients who spontaneously clear acute HCV infection, this occurs within 6 months of the estimated time of infection (median, 16.5 weeks). Only 11% of those who remain viremic at 6 months will spontaneously clear the infection at a later time (Grebely, 2014). Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need antiviral



Management of Acute HCV Infection

From www.HCVGuidance.org on March 19, 2018

therapy (see [When and in Whom to Initiate HCV Therapy](#)).

Patients who spontaneously clear should not be treated with antiviral therapy. However, they should be counseled about the possibility of reinfection and tested routinely for this development if risk behaviors are ongoing (see [HCV Testing and Linkage to Care](#)). Of note, transient suppression of viremia can occur in those with acute HCV infection, even among those who progress to chronic infection. Thus, a single undetectable HCV RNA test result is insufficient to declare spontaneous clearance (see [HCV Testing and Linkage to Care](#)); (Villano, 1999); (Mosley, 2008).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, genotype 1 infection, and host genetic polymorphisms, most notably those near the IL28B gene (Kamal, 2008); (Mosley, 2008).

There is no need to alter concomitant medications that are metabolized by hepatic enzymes unless there is concern for developing acute liver failure (eg, increasing bilirubin level and INR). Acetaminophen and alcohol consumption should be avoided during acute HCV infection (Proeschold-Bell, 2012); (Dieperink, 2010); (Whitlock, 2004). Hospitalization is rarely indicated unless nausea and vomiting are severe.

Although acute liver failure is very rare (<1%), it represents a serious and life-threatening complication of acute HCV infection. Patients with an INR >1.5 and those who exhibit any signs of acute liver failure (eg, hepatic encephalopathy) should be referred to a liver transplant center immediately. The use of HCV antiviral regimens in acute liver failure should be managed by a clinician experienced in HCV treatment, ideally in consultation with a liver transplant specialist.

Antiviral Therapy

Recommended Treatment for Patients With Acute HCV Infection	
RECOMMENDED	RATING
If the clinician and patient decide that a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection).	Ila, C
If a decision is made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 to 16 weeks before starting treatment is recommended to allow time for possible spontaneous clearance.	Ila, C

Recommended Regimens for Patients With Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	Ila, C

When Antiviral Therapy Is Not Recommended	
NOT RECOMMENDED	RATING
For patients in whom HCV infection spontaneously clears, antiviral treatment is not recommended.	III, B



Management of Acute HCV Infection
From www.HCVGuidance.org on March 19, 2018

In the interferon era, the efficacy of acute HCV infection treatment (particularly for genotype 1), including abbreviated regimens, was superior to the treatment of chronic infection (Ghany, 2009). There are emerging data on the treatment of acute HCV infection with shortened courses of all-oral, DAA regimens both in HCV mono-infection and HIV/HCV coinfection. But as yet, there are insufficient data to support a particular regimen or treatment duration. Until more definitive data are available, monitoring for spontaneous clearance for a minimum of 6 months before initiating treatment is recommended. When the decision is made to initiate antiviral therapy after 6 months, treatment as described for chronic hepatitis C is recommended (see [Initial Treatment of HCV Infection](#) and [When and in Whom to Initiate HCV Therapy](#)).

There are instances wherein a clinician may decide that the benefits of early treatment outweigh waiting for possible spontaneous clearance. These include situations where importance is placed on:

- HCV transmission prevention (eg, a surgeon, a person with ongoing intravenous drug use, or an HIV-positive man who engages in sex with other men)
- Mitigation of clinical consequences (eg, a patient with cirrhosis who is acutely superinfected with HCV)
- Reduction in the likelihood of loss to follow-up (eg, a patient who may not be engaged in care in 3 to 6 months)

Referral to an addiction specialist and harm reduction counseling should be provided if relevant. If a decision is made to initiate treatment during the acute infection period, the same regimens recommended for chronic HCV infection are recommended for acute infection, given their high efficacy and safety in chronic HCV infection (see [Initial Treatment of HCV Infection](#) and [When and in Whom to Initiate HCV Therapy](#) sections).

Last update: September 21, 2017



HCV in Pregnancy

From www.HCVGuidance.org on March 19, 2018

HCV in Pregnancy

Testing

Recommendations for HCV Testing in Pregnant Women	
RECOMMENDED	RATING ³
There is no recommendation at this time for universal HCV screening in pregnant women, however this is under review.	II, C
Screening with an HCV antibody assay is recommended for pregnant women with known or suspected risk factors for HCV infection. Confirmatory HCV nucleic acid testing is recommended for women with a positive screening test.	I, A

Current US Centers for Disease Control and Prevention (CDC) screening guidelines (CDC, 1998); (Smith, 2012a) recommend that any woman—pregnant or otherwise—with a known or suspected risk factor, such as injection drug use or HIV infection, should be tested for HCV infection (see [HCV Testing and Linkage to Care](#)); (Koneru, 2016). Screening for HCV antibody should be followed by confirmatory nucleic acid testing (HCV RNA) for anyone positive on the screening assay (CDC, 2013) to differentiate past versus current, active infection. Women found to be HCV-infected should be linked to clinical care services for their infection(s) and drug dependence treatment, as needed.

With current increases in HCV infection among young adults, including women of childbearing age, there is considerable discussion about the possibility of universal screening of pregnant women (Ly, 2017). Identifying HCV as women engage in prenatal care would allow appropriate assessment of liver disease status as well as establish care for their exposed children. This public health consideration will be weighed with concerns regarding potential cost and the logistics of linking patients to care.

Whom to Treat

Recommendation Regarding HCV Treatment and Pregnancy	
RECOMMENDED	RATING ³
For women of reproductive age with known HCV infection, antiviral therapy is recommended before considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B

Not Recommended Regarding HCV Treatment and Pregnancy	
NOT RECOMMENDED	RATING ³
Treatment during pregnancy is not recommended due to the lack of safety and efficacy data.	IIb, C

**HCV in Pregnancy**

From www.HCVGuidance.org on March 19, 2018

Women of reproductive age with HCV should be counseled about the benefit of antiviral treatment prior to pregnancy to improve the health of the mother and eliminate the low risk of mother-to-child transmission (MTCT). The safety of direct-acting antivirals (DAAs) in pregnancy is unknown, and there are no data on the effect of DAAs on male or female fertility. However, ribavirin is contraindicated in pregnancy due to its known teratogenicity. In addition, the risk for teratogenicity persists for up to 6 months after ribavirin cessation and applies to women taking ribavirin and female partners of men taking ribavirin. Women who become pregnant while on DAA therapy (with or without ribavirin) should discuss the risks versus benefits of continuing treatment with their physicians. If exposed to ribavirin, they should also have their maternal and fetal outcomes reported to the [ribavirin pregnancy registry](#) (see also, [Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin](#)).

Monitoring During Pregnancy

Recommendations for Monitoring HCV-Infected Women During Pregnancy	
RECOMMENDED	RATING
HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody-positive pregnant women to assess the risk of mother-to-child transmission (MTCT) and degree of liver disease.	I, B
All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT.	I, B
In HCV-infected pregnant women with pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy (ICP) with subsequent assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bile acids.	I, B
HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine (ie, high-risk pregnancy) obstetrician.	I, B

Pregnancy Impact on HCV Infection

Pregnancy itself does not appear to negatively affect chronic HCV infection. In general, serum ALT levels decrease during the first and third trimesters of pregnancy and increase after delivery. HCV RNA levels rise during the first and third trimesters, reaching a peak during the third trimester, and decrease postpartum (Conte, 2000); (Gervais, 2000). These effects are likely due to the immunosuppressive effects of pregnancy. HCV-infected pregnant women have a higher incidence of intrahepatic cholestasis of pregnancy (ICP) (pooled OR 20.40 [95% CI, 9.39-44.33, I²=55%]) based on a meta-analysis of 3 studies when compared to noninfected pregnant women (Wijarnpreecha, 2017). ICP is associated with an increased rate of adverse maternal and fetal outcomes; all patients with this syndrome should be immediately referred to a high-risk obstetrical specialist for monitoring and treatment.

HCV Infection Impact on Pregnancy and Perinatal Outcomes

Although some studies show an increased risk of adverse perinatal outcomes (eg, preterm delivery, low birth weight infants, and congenital anomalies) with maternal HCV infection, these risks are confounded by comorbid conditions, such as substance use (Cornell, 2011). However, pregnant women with cirrhosis are at increased risk for poor maternal outcomes (ie, preeclampsia, cesarean section, hemorrhagic complication, and death) and neonatal outcomes (ie, preterm delivery, low birth weight, and neonatal death) (Puljic, 2016); (Tan, 2008). Women with cirrhosis should be counseled



HCV in Pregnancy

From www.HCVGuidance.org on March 19, 2018

about these increased risks and care should be coordinated with specialists in maternal-fetal medicine.

Hepatitis C MTCT occurs at an overall rate of 5% to 15% (Mast, 2005); (Ceci, 2001); (Shebl, 2009); (Jhaveri, 2015), with the number that progress to chronic infection being 3% to 5%. No specific risk factor predicts transmission and no specific intervention (eg, antiviral, mode of delivery, or others) has been demonstrated to reduce transmission—except for suppression of HIV replication in women with HIV/HCV coinfection (Checa Cabot, 2013). Given the potential associated risk of MTCT, it is advisable to avoid invasive procedures (eg, fetal scalp monitors and forceps delivery).

The neuropsychiatric and systemic side effects of interferon-based agents and the pregnancy category X rating of ribavirin made studies involving these drugs to interrupt MTCT untenable for safety reasons. It is important to note that DAAs have not been studied as a way to interrupt MTCT. These drugs have not demonstrated significant toxicity in animal studies, and antiviral medication use has become the standard of care for people with HIV and hepatitis B infection. Therefore, it is realistic to think that DAAs could be used in the future to interrupt MTCT. However, with a low transmission rate, improved methods to identify mothers who are likely to transmit are needed to reduce the number needed to treat below 20 to prevent 1 transmission event. DAA therapy is not recommended during pregnancy to reduce MTCT due to the current lack of safety and efficacy data.

Postpartum Issues

Recommendations Regarding Breastfeeding and Postpartum Care for HCV-Infected Women	
RECOMMENDED	RATING
Breastfeeding is not contraindicated in women with HCV infection, except when the mother has cracked, damaged, or bleeding nipples, or in the context of HIV coinfection.	I, B
Women with HCV infection should have their HCV RNA reevaluated approximately 9 to 12 months after delivery to assess for spontaneous clearance.	I, B

HCV and Breastfeeding

Breastfeeding is not a risk for HCV MTCT (CDC, 1998) with studies showing similar rates of maternal infection in breast-fed and bottle-fed infants (Best, 1998). However, given the associated risks of HCV transmission with blood exposure and HIV transmission with breastfeeding, we recommend that HCV-infected women who breastfeed abstain from doing so while their nipples are cracked, damaged, or bleeding, or in the context of HIV/HCV coinfection.

Spontaneous Clearance in the Postpartum Period

HCV RNA levels can fluctuate during pregnancy and the postpartum period. The most frequently observed pattern is a steady rise in HCV RNA levels during pregnancy followed by a slight or significant drop (>3-4 log) in the postpartum period (Lin, 2000). This is most likely due to the release of tolerance in HCV-specific T lymphocyte responses that develops during pregnancy (Honegger, 2013). Spontaneous clearance of HCV can occur in the postpartum period. Previous studies with small numbers of patients demonstrated that up to 10% of postpartum women became HCV RNA undetectable (Hattori, 2003); (Lin, 2000); (Honegger, 2013). A recent study from Egypt demonstrated a 25% rate of spontaneous resolution that was strongly associated with the favorable IL28B allele (Hashem, 2017).

Given these findings, women should have their HCV RNA reevaluated within 9 to 12 months after delivery. In that time, HCV RNA could become undetectable or rebound to prepregnancy levels. The possibility of spontaneous viral clearance should be considered for any woman who is being assessed for DAA treatment in the postpartum period.



HCV In Pregnancy

From www.HCVGuidance.org on March 19, 2018

Last update: September 21, 2017



HCV in Children

From www.HCVGuidance.org on March 19, 2018

HCV in Children

Testing

Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of HCV-Infected Children	
RECOMMENDED	RATING [Ⓢ]
All children born to HCV-infected women should be tested for HCV infection. Testing is recommended using an antibody-based test at or after 18 months of age.	I, A
Testing with an HCV RNA assay can be considered in the first year of life, but the optimal timing of such a test is unknown.	IIa, C
Repetitive testing by HCV RNA is not recommended.	III, A
Children who are anti-HCV positive after 18 months of age should be tested with an HCV RNA assay after age 3 to confirm chronic hepatitis C infection.	I, A
The siblings of children with mother-to-child transmission acquired chronic HCV should be tested for HCV infection using anti-HCV antibody testing.	I, C

Although the prevalence of chronic HCV is lower in children than adults, an estimated 5 million children worldwide have active HCV infection (Gower, 2014). Data from the National Health and Nutrition Examination Survey (NHANES) collected between 2003 and 2010 indicates that 0.2% of 6- to 11-year-olds (31,000 children) and 0.4% of 12- to 19-year-olds (101,000 adolescents) in the US are chronically infected with HCV (Denniston, 2014).

As birth to an HCV-infected mother is a known risk for infection, such offspring should be evaluated and tested for HCV. The rate of mother-to-child transmission (MTCT) of HCV infection is approximately 5%, although rates are higher among women with inadequately controlled HIV coinfection, and women with higher HCV RNA levels, or viral loads (>6 log IU/mL) (Benova, 2014); (Delotte, 2014); (Coltrell, 2013). Identifying, following, and treating exposed children is recommended. The basis for evaluation early in life is HCV RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months. About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 3 years of age (EPHCVN, 2005); (Mast, 2005).

There is considerable debate about the utility of HCV RNA testing within the first year of life. Proponents argue that use of a highly sensitive RNA assay early in life can increase the rate of infected infants detected, and that a negative result strongly suggests the infant is not infected while a positive result helps identify HCV cases earlier. Opponents argue that early testing does not change the need for definitive testing at or after 18 months; HCV RNA is more expensive than an antibody-based test; and there is no intervention or treatment that will occur prior to age 3—because of lack of approved drugs for this age group and to allow for possible spontaneous clearance. On balance, optional early HCV RNA testing may facilitate more infants getting tested and retained in care if they are positive. The optimal timing of HCV RNA testing is still unknown, but 2 to 6 months after birth is reasonable. There is no value in repeated HCV RNA testing prior to 18 months of age, but anti-HCV testing should take place at or after 18 months of age.



HCV in Children

From www.HCVGuidance.org on March 19, 2018

Transmission and Prevention

Recommendations for Counseling Parents Regarding Transmission and Prevention in HCV-Infected Children	
RECOMMENDED	RATING
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, HCV-infected children do not pose a risk to other children and can participate in school, sports, and athletic activities, and engage in all other regular childhood activities without restrictions.	I, B
Parents should be informed that universal precautions should be followed at school and in the home of children with HCV infection. Educate families and children about the risk and routes of HCV transmission, and the techniques for avoiding blood exposure, such as avoiding the sharing of toothbrushes, razors, and nail clippers; and the use of gloves and dilute bleach to clean up blood.	I, B

HCV-infected children often face discrimination and stigmatization in school and child-care settings that is driven by inadequate public understanding of hepatitis C. HCV is not transmitted by casual contact in the absence of blood exposure. Families should not be forced to disclose a child's HCV infection status, and children should not be restricted from any routine childhood activity.

The risk of sexual transmission of hepatitis C is considered very low/rare. Sexual transmission occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men (see [HCV Testing and Linkage to Care](#)) ([Schmidt, 2014](#)). Adolescents with HIV infection and those with multiple sexual partners or sexually transmitted infections (STIs) should be encouraged to use barrier precautions to prevent sexual transmission of HCV and other STIs. Other adolescents with HCV infection should be counseled that the risk of sexual transmission is low but barrier precautions are recommended for other reasons (see [Testing and Linkage to Care: Table 2 - Measures to Prevent Transmission of HCV](#)).



HCV in Children

From www.HCVGuidance.org on March 19, 2018

Monitoring and Medical Management

Recommendations for Monitoring and Medical Management of HCV-Infected Children	
RECOMMENDED	RATING ³
Routine liver biochemistries at initial diagnosis and at least annually thereafter are recommended to assess for disease progression.	I, C
Appropriate vaccinations are recommended for HCV-infected children not immune to hepatitis B virus and/or hepatitis A virus to prevent these infections.	I, C
Disease severity assessment via routine laboratory testing and physical examination, as well as use of evolving noninvasive modalities (ie, elastography, imaging, or serum fibrosis markers) is recommended for all children with chronic HCV.	I, B
Children with cirrhosis should undergo hepatocellular carcinoma (HCC) surveillance and endoscopic surveillance for varices per standard recommendations.	I, B
Hepatotoxic drugs should be used with caution in children with chronic HCV after assessment of potential risk versus benefit of treatment. Use of corticosteroids, cytotoxic chemotherapy, or therapeutic doses of acetaminophen are not contraindicated in children with chronic HCV.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic HCV.	II, C
Anticipatory guidance about the potential risks of ethanol for progression of liver disease is recommended for children with HCV and their families. Abstinence from alcohol and interventions to facilitate cessation of alcohol consumption, when appropriate, are advised for all persons with HCV infection.	I, C

In children, liver disease due to chronic HCV infection generally progresses slowly, and cirrhosis and liver cancer are infrequently encountered. Although elevated serum aminotransferase levels are often noted, HCV-infected children younger than 3 years virtually never have advanced liver disease.

The initial assessment of children with chronic HCV infection includes exclusion of other causes of liver disease, assessment of disease severity, and detection of extrahepatic manifestations of HCV. Testing for concomitant HBV (HBsAg, anti-HBc, and anti-HBs), HIV (anti-HIV), and immunity to HAV (anti-HAV IgG) are recommended due to shared risk factors and the need to vaccinate all nonimmune children that may not have received routine childhood vaccines against HAV and HBV.

Disease staging in children can be accomplished via physical examination and the assessment of routine laboratory parameters including albumin, serum aminotransferase levels, total bilirubin, international normalized ratio (INR), and platelet count every 6 to 12 months. Serum fibrosis markers also hold promise to stratify disease severity but require further validation (Mack, 2012). Of note, serum aminotransferase levels are not consistently reflective of disease severity in children. In one study nearly 33% of children had normal aminotransferase levels despite substantial necroinflammation on biopsy (Casiraghi, 2004).



HCV in Children

From www.HCVGuidance.org on March 19, 2018

For children in whom advanced liver disease is a concern, liver imaging to evaluate for splenomegaly or venous collaterals is recommended initially, using liver ultrasound instead of CT or MRI due to its widespread availability and lack of ionizing radiation. Although liver biopsy is considered the gold standard regarding the grade of inflammation and stage of fibrosis, sampling artifact is problematic and most patients and practitioners prefer noninvasive alternatives, such as liver elastography, to determine the presence/absence of cirrhosis, particularly in children. Ultrasound-based liver elastography in children requires the use of specialized probes and cutoff values for advanced fibrosis/cirrhosis that differ from those used in adults, but this approach appears promising for monitoring children with chronic HCV infection ([Behairy, 2016](#)); ([Geng, 2016](#)); ([Lee, 2013](#)).

Due to the slow rate of fibrosis progression among children, there are few, if any, established bona fide risk factors for disease progression. Development of advanced liver disease in children is infrequent until more than 30 years of infection ([Jhaveri, 2011](#)); ([Goodman, 2008](#)); ([Minola, 2002](#)). However, as in adults, children with comorbid disease—such as obesity with nonalcoholic fatty liver disease and congenital heart disease with elevated right heart pressures—and those receiving hepatotoxic drugs should be monitored carefully for disease progression.

Hepatocellular carcinoma (HCC) is rarely encountered among children and has been reported almost exclusively in children with cirrhosis. There are reports that children with chronic HCV and a history of childhood leukemia may be at increased risk of developing HCC, but evidence is limited ([González-Peralta, 2009](#)). In children with cirrhosis, liver ultrasound with or without serum alpha-fetoprotein (AFP) testing every 6 months is recommended for HCC surveillance per AASLD guidelines ([Bruix, 2011](#)). A baseline endoscopy is advisable to detect esophageal varices in children with cirrhosis and every 3 years thereafter in the absence of antiviral therapy. After successful antiviral therapy, the risk for cirrhosis complications is substantially less.

In children with advanced fibrosis from chronic HCV, medications that are known to accelerate hepatic fibrosis (eg, methotrexate) should be avoided if possible. Similarly, abstinence from alcohol use is strongly advised to minimize disease progression. Although corticosteroids and other immunosuppressants may enhance HCV replication, they are not contraindicated in children with HCV and should be prescribed for appropriate indications based on overall risk vs benefit. Of note, icteric flares of HCV—as reported in children and adults with chronic HBV—have not been reported in children receiving organ transplants or cytotoxic chemotherapy. Although underlying liver disease is a risk factor for development of sinusoidal obstruction syndrome following bone marrow transplantation, the presence of HCV infection should not delay this therapy.

To remain well, untreated children with chronic hepatitis C are encouraged to maintain a healthy body weight due to the known deleterious effects of insulin resistance on fibrosis progression with HCV infection. Other commonly used medications, such as antimicrobial agents, antiepileptics, and cardiovascular agents, should be dosed per standard recommendations. However, NSAIDs and aspirin should be avoided, if possible, in children with cirrhosis and esophageal varices due to concerns of gastrointestinal bleeding and nephrotoxicity. Acetaminophen is a safe and effective analgesic for children with chronic HCV infection when dosed per package insert recommendations.

**HCV in Children**

From www.HCVGuidance.org on March 19, 2018

Treatment

Recommendations for Whom and When to Treat Among HCV-Infected Children	
RECOMMENDED	RATING ^a
If direct-acting antiviral (DAA) regimens are available for a child's age group, treatment is recommended for all HCV-infected children older than 3 years as they will benefit from antiviral therapy, independent of disease severity.	I, B
Treatment of children aged 3 to 11 years with chronic hepatitis C should be deferred until interferon-free regimens are available.	II, C
The presence of extrahepatic manifestations—such as cryoglobulinemia, rashes, and glomerulonephritis—as well as advanced fibrosis should lead to early antiviral therapy to minimize future morbidity and mortality.	I, C

Recommended regimens listed by evidence level and alphabetically for Adolescents ≥ 12 Years Old or Weighing ≥ 35 kg, Without Cirrhosis or With Compensated Cirrhosis		
RECOMMENDED	DURATION	RATING ^a
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naïve without cirrhosis or with compensated cirrhosis ^a , or treatment-experienced ^b without cirrhosis	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-experienced ^b with compensated cirrhosis ^a	24 weeks	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin ^c for patients with genotype 2 who are treatment-naïve or treatment-experienced ^b without cirrhosis or with compensated cirrhosis ^a	12 weeks	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin ^c for patients with genotype 3 who are treatment-naïve or treatment-experienced ^b without cirrhosis or with compensated cirrhosis ^a	24 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naïve or treatment-experienced ^b without cirrhosis or with compensated cirrhosis ^a	12 weeks	I, B
^a Child-Pugh A ^b Patients who have failed an interferon-based regimen, with or without ribavirin ^c See ribavirin dosing table for recommended weight-based dosages.		

**HCV in Children**

From www.HCVGuidance.org on March 19, 2018

Table. Dosing for Ribavirin in Combination Therapy With Sofosbuvir for Adolescents ≥ 12 Years Old or Weighing ≥ 35 kg

Body Weight (kg)	Daily Ribavirin Dosage (in 2 divided doses)
<47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
>80	1200 mg/day

Advanced liver disease due to HCV infection is uncommon during the childhood years. However, liver disease progresses over time with increasing fibrosis severity. Although uncommon, cirrhosis is occasionally seen in infected children and adolescents younger than 18. Children have a long life expectancy during which HCV complications may develop. Infected children and adolescents may also transmit HCV to others.

DAA regimens have a very high success rate in adults with chronic HCV infection. In addition, interferon-based regimens have limited success in children with genotype 1 or 4 infection. Interferon and ribavirin have general and pediatric-specific toxicities (eg, temporary growth impairment) that do not occur with DAA regimens. Several clinical trials are underway, early data have been published, and DAA regimens are now available for adolescents 12 years and older. It is anticipated that additional safe and effective DAA regimens will be available for children aged 3 through 11 in the near future.

In a phase 2, multicenter open-label study of 100 adolescents with chronic genotype 1 infection treated for 12 weeks with the adult formulation of ledipasvir-sofosbuvir, sustained virologic response (SVR) was documented in 98% of participants (Balistreri, 2017). The two patients who did not achieve SVR12 were lost to follow-up during or after treatment. Most of the patients were treatment naive (80%). One patient had cirrhosis, 42 did not, and the cirrhosis status was unknown in the remaining 57. The regimen was safe and well tolerated in this population, and the adult dosage formulation resulted in pharmacokinetic characteristics similar to those observed in adults.

The combination of sofosbuvir and ribavirin at doses approved for adults was tested in adolescents with chronic genotype 2 (12 weeks of treatment) or genotype 3 (24 weeks of treatment) infection (Wirth, 2017). Of the 52 adolescents, 75% had genotype 3 infection, and 83% were treatment naive. Cirrhosis status was negative in 40% and unknown in 60% of the participants. SVR12 rates were 100% (13/13) and 97% (38/39) in genotype 2 and 3 infections, respectively. This regimen was safe and well tolerated, and pharmacokinetic properties of sofosbuvir were equivalent to those observed in adults.

Last update: September 21, 2017



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From www.HCVGuidance.org on March 19, 2018

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